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PATENT- OG VAREMÆRKESTYRELSEN

pH AND TIME CONTROLLED DRUG DELIVERY SYSTEM FOR COLON DELIVERY

FIELD OF THE INVENTION

The present invention relates to a novel drug delivery system especially suitable for delivering therapeutically, prophylactically and/or diagnostically active substance to specific parts of the gastrointestinal tract such as, e.g., the colon. The drug delivery system is designed so that the release of the active substance is delayed by a combination of two principles, namely by combination of a pH controlled and a time controlled mechanism. Furthermore, after the release delay, the drug delivery system is designed to release the active substance relatively fast to ensure that the active substance is ready for absorption via the colon mucosa and/or ready for exertion its effect locally in the colon.

BACKGROUND OF THE INVENTION

During the last decades it has emerged that some active substances are subject to colon absorption. Furthermore, a number of active substances exert their effect locally in the colon. Thus, research and development have aimed at developing suitable delivery systems for targeting active substances to the colon.

To this end a number of formulations have been suggested such as, e.g., a so-called time-controlled explosion system (TES) developed by Fujisawa (see e.g. EP-B-0210 540). Kinget et al. in J. Drug Targeting 1998, **6**, 129-149, Leopold in PSTI 1999, **2**, 197-204 and Bussemer et al. in Critical Review in Therapeutic Drug Carrier Systems 2001, **18**, 433-455 have given reviews on dosage forms for colon-specific drug delivery.

However, the known delivery systems for colon delivery result in relatively slow release of the active substance after a certain lag time. Such systems are therefore not particularly suitable in situations where it is desired to have a relatively fast release of the active substance in the colon. A relatively fast release of the active substance in the colon is especially of an advantage in those cases where the active substance is only absorbed in the ascending part of the colon or is poorly soluble and therefore requires a substantial amount of water/fluid to dissolve before absorption. Another situation is when the effect of the active substance is limited to a certain time period or when the absorption from the colon is poorer that from the small intestine. Furthermore, the active substance may exert its effect locally in the colon or other parts of the gastrointestinal system.

Furthermore, the absorption of some active substances takes place in a specific part of the small intestine, i.e. they have a very narrow absorption window. For such substances it is also an advantage to develop a delivery system from which a fast release of the active substance takes place at a predetermined time corresponding to the time it takes to reach the specific part of the gastrointestinal tract that enables absorption of the active substance.

DESCRIPTION OF THE INVENTION

The present invention provides a drug delivery system that provides a predetermined lag time before the active substance is released. The lag time obtained is based on a combination of two principles, namely a combination of a pH dependent release and a pH independent, but time controlled release.

In contrast to many of the known colon delivery systems, the drug delivery system according to the present invention is contemplated to be suitable for large-scale production.

Thus, the present invention provides a pH and time-controlled drug delivery system for oral use comprising one or more of a first type of unit, the first type of unit comprising a therapeutically, prophylactically and/or diagnostically active substance, and the first type of unit having a layered structure of at least

i) an inner core
ii) a time-controlled layer surrounding the inner core,
iii) a film coating applied on the time-controlled layer, wherein the film coating is substantially water insoluble but permeable to an aqueous medium, and
iv) an outer layer of an enteric coating,

wherein the release of the active substance from the unit - when tested *in vitro* as an average of at least six determinations - is not more than about 10% w/w at a first pH value below about 4.0, and at a second pH value of from about 5.0 to about 8.0 the active substance is released in such a manner that - after a lag time of from about 0.5 to about 8 hours in which first time period not more than about 10% w/w of the active substance is released - at least about 50% w/w of the active substance contained in the unit is released within a second time period of not more than about 2 hours.

The drug delivery system may be in the form of a multiple unit composition comprising a multiplicity of individual units or it may be in the form of a single unit composition. In the case of a multiple unit composition, the drug delivery system may contain more than one type of unit. Thus, in order to obtain a composition with a specific release pattern of the active substance, the delivery system may contain a mixture of two or more types of units each having a specific release pattern of the active substance. For instance in certain cases a suitable pharmaceutical composition may comprise a mixture of e.g. three different types of units each containing the same active substance. The first type of unit may be designed to release the active substance almost immediately upon administration. The second type of unit may be designed to release the active substance in a sustained manner in order to produce a relatively constant plasma concentration in a predetermined time period and, finally, the third type of unit may be designed to release the active substance in the colon or in specific part of the intestine where the absorption of the active substance is favored.

The design of the drug delivery system is relatively simple and makes it easy to design pharmaceutical compositions that e.g. have two or more, the same or different, active substance contained in one or more types of units or, alternatively, present in two or more, the same or different, layer of a unit.

More specifically, in a drug delivery system according to the invention, the release of the active substance from the unit – when tested *in vitro* – is not more than about 7.5% w/w such as, e.g., not more than about 5% w/w, not more than about 4% w/w, not more than about 3% w/w, not more than about 2% w/w or not more than about 1% w/w at the first pH value below about 4.0. In specific embodiments of the invention, the first pH value is below about 3.5, such as, e.g., below about 3.0, below about 2.5, below about 2.0, below about 1.5 or a pH value corresponding to that of 0.1 N HCl.

As mentioned above, the lag time is from about 0.5 to about 8 hours. In specific embodiments, the lag time is from about 1.0 to about 7 hours such as, e.g., from about 1.5 to about 6 hours, from about 2.0 to about 5 hours or from about 2.5 to about 4.5 hours or from about 2.5 to about 4 hours. In those cases where the drug delivery system is intended for delivering an active substance to the colon, the lag time is normally from about 2.5 to about 4.5 hours. However, as will be discussed herein later, a drug delivery system of the present invention is also suitable for use in those cases where the active substance is absorbed from a specific part of the small intestine. In such cases, the lag time is shorter than when colon absorption or delivery is the target.

An important feature of a drug delivery system of the present invention is that the active substance is relatively fast released after the predetermined lag time. Furthermore, the drug delivery system should be designed to release all or almost the whole content of active substance.

Accordingly, after the above-mentioned lag time - at least about 60% w/w such as, e.g., at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w or at least about 90% w/w of the active substance contained in the unit is normally released within the second time period of not more than about 2 hours.

In specific embodiments, the said second time period is not more than about 90 min such as, e.g., not more than about 60 min, not more than about 50 min, not more than about 45 min, not more than about 40 min, not more than about 35 min, not more than about 30 min, not more than about 25 min, not more than about 20 min, not more than about 15 min, not more than about 10 min of not more than about 5 min. Normally the second time period is about 30-60 min.

A drug delivery system according to the present invention may contain one or more active substances contained in one or more different types of units.

The active substance is contained in the unit in one or more of the layers i) - iii) and/or in a further layer v) surrounding the inner core. In a specific embodiment of the invention the active substance is contained in the further layer v) and normally, the further layer v) is situated between layer i) and ii).

As mentioned above, a drug delivery system according to the invention is especially suitable when the active substance is subject to colon absorption and/or exerts its effect in the colon.

The present inventors have found that in order to obtain a drug delivery system that enables a predetermined delay in the release of the active substance and at the same time enables a relatively fast release of the active substance after the predetermined delay, it is suitable to take advantage of two different principles for delaying the release of the active substance, namely one principle for the delay in those parts of the gastrointestinal tract wherein the pH is in the acidic region and another principle for the

delay in those parts of the gastrointestinal tract, wherein the pH is in the neutral and alkaline region.

The principle employed in those parts of the gastrointestinal tract wherein the pH is in the acidic region is based on the enteric coating principle, i.e. the possibility of providing a coating that is substantially insoluble in an acidic environment, but which is soluble in a neutral and alkaline environment. This is achieved by use of so-called enteric polymers, which are insoluble in acidic media, but soluble in neutral and alkaline media. Accordingly, the release is dependent on a shift of pH from the acidic region to the neutral/alkaline region.

The individual and interindividual variations with respect to gastric emptying are therefore of minor importance when a drug delivery system according to the invention is applied. Furthermore, in those cases, where the drug delivery system is in the form of a multiple unit composition the gastric transit time of the multiple units is normally relatively independent of whether the patient is in fasted or fed state. This is in contrary to what is generally seen when a single unit composition is administered.

In a specific embodiment of the invention, the enteric polymer employed is a polymer that has a pH cut off that enables the start of the dissolution of the enteric coating at the time when the delivery system enters the small intestine. In the present context the term "pH cut off" is defined as the lowest pH value by which the enteric polymer is soluble at a temperature of 37 °C. In contrast to the transit time in the stomach, the transit time in the small intestines is relatively constant (3-5 hours). The present inventors have therefore found that it is an advantage to design a delivery system that independently of the transit time in the stomach has properties that governs when the release of the active substance takes place after entering into the small intestine.

The principle employed in those parts of the gastrointestinal tract, wherein the pH is in the neutral/alkaline region, is based on a time controlled release. Whereas the pH in the stomach normally is about 1.5-2.0 for fasted conditions and about 3.0-5.0 for fed conditions, the pH of the small intestine is about 5.0-6.5 in the jejunum, about 6.0-7.5 in the ileum and about 6-8 in the colon. The variation of pH in the intestine is difficult to use from a pharmaceutical formulation point of view, but the relatively constant transit time in the small intestine is a much more favorable approach. Accordingly, a drug delivery system according to the present invention is designed so that after entry into the small intestines the enteric coat is relatively fast dissolved and a time controlled process is

started by which the time controlled layer contained in the unit is controllable subject to a process that results in the breakage of the film coating layer. In those cases where the time controlled layer is a swellable layer, the layer starts to swell. At a certain point in time the swellable layer has swelled to such an extent that the film coating layer, that coats the swellable layer, breaks, disrupts or is otherwise destroyed. Then the active substance contained in the unit becomes exposed to the gastrointestinal tract and is ready to be absorbed or to exert its effect either immediately or later.

pH dependent release - enteric coating

As mentioned above, the unit(s) contained in a drug delivery system of the present invention is (are) coated with an enteric coating. Normally, this coating is the outermost layer of the unit(s).

As mentioned above, the term "pH cut off" is intended to indicate the lowest pH value at which the enteric polymer is soluble at a temperature of 37 °C.

The pH cut off of the enteric polymer is important in order to ensure that the enteric coating is dissolved as quickly as possible after entering of the drug delivery system into the small intestine.

Accordingly, the enteric coating for use in the present invention comprises an enteric polymer that has a pH cut off of at the most about 8.0 such as, e.g. in a range of from about 4 to about 7.5, in a range of from about 4.5 to about 7.0, from about 4.9 to about 6.9, from about 5.0 to about 6.5, from about 5.0 to about 6.3, from about 5.0 to about 6.0, from about 5.0 to about 5.9, from about 5.0 to about 5.7, from about 5.0 to about 5.6 or from about 5.0 to about 5.5.

The enteric coating used according to the invention comprises an enteric polymer. Suitable enteric polymers are selected from the group consisting of:
Amylose acetate phthalate, cellulose acetate phthalate CAP (pH cut off about 6.2), cellulose acetate succinate, cellulose acetate trimellitate CAT (pH cut off about pH 5.0), carboxymethyl ethylcellulose, formalin treated gelatine, hydroxypropyl methylcellulose acetate succinate HPMCAS (pH cut off about 5.0-5.5), hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose phthalate HPMC-P (pH cut off about 5.0 and about 5.5), methacrylic acid copolymer (Eudragit L) (pH cut off about 5.5 and about 6), methacrylic acid copolymer (Eudragit S) (pH cut off about 7), methacrylic acid copolymer (Eudragit FS) (pH cut off about 7.5), polyvinyl acetate phthalate PVAP

(sureteric), shellac, starch acetate phthalate, styrene-Maleic acid copolymer, zein, and mixtures thereof.

Normally, the concentration of the enteric polymer used is in a range corresponding to about 2 to about 60% w/w based on the total weight of the unit. The enteric coating may also contain additives like those mentioned herein later. Thus, e.g. plasticizers etc. may be suitable as additives.

The application of the enteric coat is normally a last step in the preparation of the drug delivery system according to the invention. However, a further layer may be applied, e.g. containing an active substance.

As will be discussed in more detail below in the paragraph denoted "Preparation of a drug delivery system", it is generally necessary to provide the enteric coating by use of a solution or dispersion of the enteric polymer in a solvent that mainly contains organic solvents. If a water-based solvent is employed, precautions may be taken to avoid that it initiates the swellable layer to swell already during the manufacturing process and, accordingly, the desired and predetermined time dependent release after administration may be severely impaired. The organic based solvent may, however, contain some water or aqueous medium provided that it does not impair the swelling ability of the swellable layer. The same applies to any other layer present in the unit such as, e.g., the time-controlled layer.

The cores

The inner core of a drug delivery system according to the invention may be an inert core or a core containing the active substance. It may also be in the form of a pellet, granules, granulates or a tablet. In the latter case, the drug delivery system is presented in the form of a single unit composition.

Examples of a core suitable for use according to the invention are, e.g., calcium alginate beads, cellulose spheres, charged resin spheres, glass beads, polystyrene spheres, sand silica beads or units, sodium hydroxide beads, sucrose spheres, collagen-based beads and crystals of an active substance.

In specific embodiments the core is selected from cellulose spheres and sucrose spheres. The cellulose spheres may be obtained from:

- Asahi Kasei Corporation

- IPC Process Center eller Syntapharm
- NP Pharm

The sucrose spheres may be obtained from:

- Hanns G. Werner
- Penwest
- NP Pharm

In another specific embodiment, the core is a collagen-based core comprising collagen. The collagen-based bead is generally made of material derived from animals such as, e.g., horses, pigs, cows, etc., or from synthetic or semi-synthetic material. A suitable material for use is e.g. the collagen material disclosed in and prepared according to WO 02/070594 (Nycomed Pharma AS; entitled: "A method of preparing a collagen sponge, a device for extracting a part of a collagen foam, and an elongated collagen sponge"). The collagen material may be transformed into beads e.g. by means of lyophilization. The collagen core may have a form of a core, a sponge or foam, and it may be in a relatively non-porous form or it may also be porous. In the latter case, such a material is suitable for inclusion of e.g. an active substance within the material.

In the case of a multiple unit composition, the particle size of the core is generally from about 100-1400 μm such as, e.g. from about 150 μm to about 1200 μm, from about 200 μm to about 1200 μm, from about 200 μm to about 1000 μm, from about 250 μm to about 800 μm or from about 300 μm to about 750 μm. In a specific embodiment of the invention the particle size of the core is at the most about 500 μm to about 1000 μm, or from about 350 μm to about 500 μm.

In some cases the particle size may be at the most about 2 mm.

The density of the core is generally below about 3 g/cm^3 such as, e.g., below about 2.8 g/cm^3, below about 2.5 g/cm^3, below about 2.3 g/cm^3, below about 2.0 g/cm^3, below about 1.8 g/cm^3, below about 1.75 g/cm^3, below about 1.6 g/cm^3 or below about 1.55 g/cm^3. In the case of sucrose or cellulose based beads, the density is generally about 1.5 g/cm^3. However, the two different types of beads behave very different in a coating process, which may be related to the difference in physico-chemical properties (hydrophilicity, water content etc.). Accordingly, the coating conditions may be adjusted to each specific core material employed. In the examples herein specific conditions are given that lead to suitable results.

In general, a person skilled in the art can find guidance and advice of how to formulate and perform individual process step in Remington's Pharmaceutical Handbook to which reference is made.

Time controlled release

The time controlled release that is intended to start when the delivery system enters the small intestine is based on the idea that a film coating layer to a certain degree essentially prevents any active substance to be release from the composition until the film coating layer is impaired. The properties of the film coating layer is that it is essentially insoluble in water or aqueous media, but it permits penetration of water or aqueous media into the composition (but not as long the enteric coating is present; the enteric coating is essentially not permeable to water). The water or aqueous media that diffuse into the system may dissolve some of the active substance that is contained within or inside the film coating layer and an outward oriented diffusion process of the active substance may be operating. However, if this is the case, the end result must be that the transport of active substance out of the system via the film coating is very slow and at the most about 10% w/w of the active substance is released by such a process.

The time controlled layer may comprise a substance that is swellable, osmotic and/or effervescent. In a specific embodiment, the time controlled layer is a swellable layer.

The purpose of the time controlled layer is that upon entering of water into the layer, a process starts that results in disruption or breakage of the film coating membrane. The mechanism by which this process operates may be a swelling process, an osmotic pressure driven process and/or a process based on effervescence. A combination of these mechanisms may also be operating.

The intrusion of water into the time controlled layer may also start the dissolution process of an active substance contained in the layer or in another layer inside the time. This may be an advantage in those cases where the active substance is not readily soluble in water or where it has a relatively slow dissolution rate.

The intention of the combination of a time controlled layer such as, e.g., a swellable layer and a film coating layer is that a swelling process of the swellable layer starts when the water or aqueous media starts to diffuse into the system through the film coating. The swellable layer is able to adsorb/absorb a specific amount of water and to expand in size.

When a certain size of the swellable layer is obtained, the film coating will no longer be flexible enough to withstand any disruption and it will break, explode or be destroyed.

In this manner a predetermined lag time may be obtained by controlling the time it takes for the swellable layer to swell to such an extent that the film coating layer is disrupted or destructed. In the case of an osmotically active layer (in those cases where the time controlled layer predominantly contains an osmotically active substance) and an effervescent active layer, the end result is the same as mentioned above, namely disruption or breakage of the film coating layer.

The lag time may be adjusted by careful selection of i) the specific composition of the time controlled layer, ii) the thickness or amount of the time controlled layer, iii) the specific composition of the film coating layer and/or iv) the thickness of the film coating layer. Suitable additives may be added to the time controlled layer and/or the film coating layer in order to adjust the lag time.

In a delivery system according to the invention, the film coating normally comprises a water insoluble polymer selected from the group consisting of:
Ammonio methacrylate copolymer (Eudragit RL, Eudragit RS), cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose butyrate, cellulose propionate, cellulose valerate, crospovidone, ethyl cellulose, hydroxypropylcellulose, hydroxyethylcellulose, polyacrylate dispersion (Eudragit NE), polydiethylaminomethylstyrene, polymethylstyrene, polyvinyl acetate, polyvinyl formal, polyvinyl butyryl, wax, and mixtures thereof

In a specific embodiment, the water insoluble polymer creates a relatively non-flexible film coating. This may be obtained by application of a polymer that has a relatively short chain length and/or by avoiding any or excessive amount of plasticizer.

In a further embodiment, the film coating layer iii) comprises ethyl cellulose and/or hydroxypropylcellulose. As mentioned above, short chain length polymers are suitable for use such as, e.g., ethyl cellulose that has a viscosity of at the most about 20 cps.

In a specific embodiment of the invention, the film coating layer iii) comprises ethyl cellulose.

In those cases, where it is desired to ensure a fast destruction of the film coating layer when the swellable layer has exceeded a certain size, it may be suitable to employ a film coating layer iii) that further comprises an additive that promotes disruption or destruction of the film coating layer upon exposure to an aqueous medium.

Suitable additives may be selected from the group consisting of:
Acetylated monoglyceride, acetyltributyl, acetyltributyl citrate, acetyltriethyl citrate, benzyl benzoate, calcium stearate, castor oil, cetanol, chlorebutanol, colloidal silica dioxide, dibutyl phthalate, dibutyl sebacate, diethyl oxalate, diethyl malate, diethyl maleate, diethyl malonate, diethyl fumarate, diethyl phthalate, diethyl sebacate, diethyl succinate, dimethylphthalate, dioctyl phthalate, glycerin, glyceroltributyrate, glyceroltriacetate, glyceryl behanate, glyceryl monostearate, hydrogenated vegetable oil, lecithin, leucine, magnesium silicate, magnesium stearate, paraffin, polyethylene glycol, propylene glycol, polysorbate, silicone, stearic acid, talc, titanium dioxide, triacetin, tributyl citrate, triethyl citrate, zinc stearate, wax, and mixtures thereof.

In a specific embodiment, a suitable additive is a polyethylene glycol, magnesium stearate and/or paraffin. The polyethylene glycol may be, e.g., PEG 200, 300, 400, 540, 600, 900, 1000, 1450, (1500) 1540, 2000, 3000, 3350, 4000, 4600, 6000, 8000, 20000, or 35000 PEGs having a molecular weight of from about 200 to about 600 are liquids, whereas PEGs having a molecular weight of 1000 and above are solids.

The time controlled layer ii) of a drug delivery system of the invention normally comprises a swelling agent, an osmotically active agent and/or an effervescent agent.

The time controlled layer can also comprise one or more pharmaceutically acceptable excipients.

A swelling agent for use according to the invention may be selected from the group consisting of:
Alginic acid, alginates, carboxymethylcellulose calcium, carboxymethylcellulose sodium (Ac-Di-Sol), crospovidone, hydroxypropylcellulose, hydroxypropylmethylcellulose (HPMC), low substituted hydroxypropylcellulose (L-HPC), microcrystalline cellulose, polacrilin potassium, polyacrylic acid, polycarbofil, polyethylene glycol, polyvinylacetate, polyvinylpyrrolidone, polyvinylpyrrolidone, plasdone, sodium croscarmellose, sodium starch glycolate (Explotab), starches, and mixtures thereof.

In those cases when the time-controlled layer ii) comprises an effervescent agent, such an agent is typically selected from alkali metal carbonates, alkali metal hydrogen carbonates, alkaline earth metal carbonates, alkaline earth metal hydrogen carbonates, citric acid, tartaric acid, fumaric acid, etc., and mixtures thereof.

When the time-controlled layer ii) comprises an osmotic agent it is e.g., sodium chloride and/or sorbitol.

Normally, the weight fraction of the time controlled layer is from about 25% to about 90% w/w based on the weight of the total unit.

Active substances

The term "active substance" encompasses the active substance in any suitable form. Thus the active substance may be present in the form of a pharmaceutically acceptable salt, complex or prodrug thereof, or, whenever relevant, it may be present in racemic or any of its enantiomeric forms. Furthermore, it may be present in solid, semi-solid or dissolved form such as, e.g. in the form of particulate material e.g. in the form of crystals or it may be present in any amorphous or polymorphous form. Furthermore it may be presented as micronised powder or in the form of a solid dispersion.

Examples of active substances for use in a drug delivery system according to the invention are generally any active substance that is therapeutically, prophylactically and/or diagnostically active.

More specifically, active substances within the below-mentioned classes are especially suitable for use in a drug delivery system according to the present invention. The specific examples of active substances mentioned below are only for illustrative purposes and are not construed to limit the invention in any way. As it also appears from the above, it is possible to include other active substances in a delivery system of the invention and such a substance can be found outside the below-given classification.

Agents where local effect in the colon are interesting

The present example illustrates a preparation of a formulation for delivery of the active substance in the proximal colon, where a local effect in the colon is the purpose.

The Anthelmic agents Mebenazole and Levamisole HCl are used as examples:

Mebenazole is a benzimidazole anthelmintic agent, active against most nematodes and some cestodes worms. The adverse-effects after the usual used therapeutic doses are mainly occurring from the gastro-intestinal tract.

Mebenazole is mainly used in the treatment of the intestinal nematode infections ascariasis (roundworm), enterobiasis (threadworm), trichuriasis (whipworm) and ancylostomiasis (hookworm) infections and is also useful in mixed infections.

The usual oral dose of Mebenazole is 100-200 mg daily. Mebenazole is poorly absorbed from the GI tract and undergoes extensively first-pass elimination, being metabolised in the liver, eliminated in the bile as unchanged drug and metabolites and excreted in the faeces. Only about 2% of the oral administered dose is excreted unchanged or as metabolites in the urine. Mebenazole is highly protein bound.

Formulating a colon specific formulation of Mebenazole the number and severity of the adverse-effects occurring from the GI-tract might be decreased.

Levamisole HCl is active against a range of worms, but is mainly used in ascariasis (roundworm), ancylostomiasis (hookworm) and necatoriasis infections. Levamisole HCl also improves the depressed immune response, and are used as adjuvant therapy for adenocarcinoma of the colon following surgery.

The usual oral dose of Levamisole is 120-300 mg daily. Levamisole HCl is rapidly absorbed from the GI-tract, it is metabolised in liver and excreted in urine and faeces. Levamisole is active against intestinal nematode worms and appears to act by paralysing susceptible worms, which are subsequently eliminated from the intestine. Adverse effects include gastrointestinal effects, headache, fever, muscle pain and haematological disturbance.

By formulating a colon specific formulation the number and severity of the adverse-effects occurring from the GI-tract when administering Levamisole orally for worm infections might be decreased.

Other examples are:

Agents for treatment of Ulcerative Colitis or Irritative Bowl Syndrome, for example: Mesalazine, Olsalazine, Sulphasalazine, Alosetron

Corticosteroids, for example:
Bethamethasone, Budesonide, Dexamethasone

Anthelmintics, for example:
Mebenazole, Levamisole HCl, Pyrantek Embonate, Praziquantel, Metrifonate, Niclosamide, Piperazine

Laxatives, for example:
Bisacodyl

Agents where colon delivery could be interesting in regards to a development of a once daily CR product

The present example illustrates a preparation of a formulation for delivery of the drug substance in the proximal colon, for substances where colon delivery is interesting in regards to develop a once daily modified release formulation.

The Antihypotensive agent Midodrine and the Antidepressant agent Imipramine both water soluble drugs are used as examples:

Midodrine is a prodrug, which is activated within the human body by a rapid enzymatic hydrolysis to release the therapeutically active metabolite desglymidodrine. Desglymidodrine acts by a stimulation of α_1 receptors. Midodrine is used in the treatment of conditions such as, e.g.,

Orthostatic regulatory disorders and dysfunctions; constitutional hypotension; symptomatic hypotension during convalescence, after surgical interventions and following child birth; hypotensive lability due to weather sensitivity and foehn complaints; difficulties in getting started in the morning; adjuvant in urinary stress incontinence (mainly 1st and 2nd degree, subdivision according to Ingelman-Sundberg); retrograde ejaculation; disorder of semen ejaculation; severe orthostatic hypotension in connection with degenerative neurological diseases; hypotension due to therapy with psychotropic drugs; reduction of blood pressure due to treatment with neuroleptics and antidepressives; intrinsic hypotension; idiopathic orthostatic hypotension; and severe orthostatic hypotension.

Furthermore, midodrine may be used to attenuate symptoms of chronic orthostatic hypotension due to autonomic failure in patients with Bradbury-Egglesten, Shy-Drager syndromes, diabetes mellitus disease and Parkinson's disease.

Midodrine may also be used for the treatment of syncope.

Midodrine is approved in a variety of European and overseas countries including the U.S.A. mainly for the treatment of orthostatic hypotension.
FDA has recommended a dosing of midodrine of up to 10 mg 3 times daily for the treatment of hypotension. According to FDA, the latest dose must not be given later than 6 pm for safety reasons in order to avoid or reduce the risk of supine hypertension. Other countries recommend that the latest dose must not be given later than 4 hours before bedtime.

Midodrine for use in stress urinary incontinence is a very promising use with a tremendous market potential also due to the ageing population. Current conservative therapeutic approaches are either α-sympathomimetics, pelvic floor exercises and estrogens and surgery, which are rather complementary than competitive.

With respect to mild to moderate form of orthostatic hypotension, midodrine has a considerably larger market potential than the severe form only.

Due to the rather short half-life of the active metabolite of approximately 3 hours midodrine normally must be administered 2-4 times daily. Considering the chronic nature of the diseases in question, which requires a long term treatment as well as the correlation between plasma levels and the incidence and severity of adverse events, the development of a modified release form is highly desired.

Imipramine has properties as a typical tricyclic antideppressant. It is used in the treatment of endogenous depression and may also be effective in some cases of reactive depression. Imipramine is readily absorbed from the GI-tract, and extensively demethylated by first-pass metabolised in the liver, to its primary active metabolite desipramine. Imipramine slowes the GI-transit time, by delaying gastric emptying time and absorption from plain formulations can be delayed.

In the treatment of depression Imipramine is administered orally as the hydrochloride, the doses are expressed in terms of Imipramine hydrochloride. The usual dose being 25 mg 3

times daily initially gradually increased to 50 mg 3-4 times daily. The elimination half-life for Imipramine is ranging from 9-28 hours.

Considering the nature of the diseases in question, which requires a long time treatment, the development of a once daily CR formulation is highly desired.

A once daily formulation of Imipramine might increase patient compliance and to obtain 24 hours coverage a formulation delivering Imipramine to the colon is necessary.

Also formulation of poorly water soluble active substances for colon delivery in regards to develop a once daily formulation is relevant. The antihypertensive agent Nifedipine is an example of such a substance.

Nifedipine is used as example; Nifedipine is a calcium-channel blocker with the peripheral and coronary vasodilator properties. Nifedipine reduces peripheral resistance, after load and blood pressure. It is administered orally in the management of hypertension and Angina Pectoris. Nifedipine is rapidly and almost completely absorbed from the GI-tract, but undergoes hepatic first-pass metabolism, resulting in a bioavailability between 45 - 75%. The elimination half-life is 2 to 5 hours.

For the treatment or prophylaxis of Angina pectoris, Nifedipine is usually administered in doses of 10 mg 3 times daily. Due to the rather short half-life of the active substance and the chronic nature of the disease in question a once daily formulation of Nifedipine is highly required and might increase patient convenience/compliance.

Agents where once daily or more frequent administration is relevant

Statins

The statins (e.g. atorvastatin, cerivastatin (rivastatin), dalvastatin, lovastatin, fluvastatin, glenvastatin, pitavastatin (itavastatin, nisvastatin), pravastatin (eptastatin, epastatin), rosuvastatin, simvastatin (epistatin, synvinolin, velostatin) and tenivastatin competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver. They are more effective than other classes of drugs in lowering LDL-cholesterol but less effective than the fibrates in reducing triglycerides and raising HDL-cholesterol.

Statins produce important reductions in coronary events, in all cardiovascular events, and in total mortality in patients aged up to 75 years with coronary heart disease (history of

angina or acute myocardial infarction) and with a total serum-cholesterol concentration of 5 mmol/l or greater. Statins should also be considered for patients who have had coronary artery bypass surgery or angioplasty, or who have other clinically overt atherosclerotic disease such as cerebrovascular disease (non-haemorrhagic stroke or transient ischaemic attacks) or peripheral vascular disease because these patients are at risk of major coronary events. Statins also reduce the incidence of non-haemorrhagic stroke when used for secondary prevention in coronary heart disease.

Statins have a role in primary prevention of coronary events in patients at increased risk. Risk of coronary events is not accurately predicted from cholesterol concentrations alone and methods that take into account factors such as smoking, hypertension and diabetes mellitus should be used to estimate risk. A statin should be considered for patients with a total serum-cholesterol concentration of 5 mmol/l or greater and a coronary heart disease risk of 30% or greater over 10 years, for primary prevention following a trial of lifestyle measures and other appropriate interventions.

For primary and secondary prevention of coronary heart disease, statin treatment should be adjusted to achieve a target total cholesterol concentration of less than 5 mmol/l (or a reduction of 20–25% if that produces a lower concentration); in terms of LDL-cholesterol, the target should be below 3 mmol/l (or a reduction of about 30% if that produces a lower concentration).

Recent evidence suggests that the use of statins may benefit all patients at high risk, including those with a total cholesterol concentration of less than 5 mmol/l; these findings are awaiting confirmation.

Bone effects

Experimental evidence based on retrospective studies suggests that the cholesterol-lowering drugs statins may increase bone formation shown by a significant increase of bone-mineral density associated with taking statins in postmenopausal women (Edwards CJ et al. Lancet 2000; 355: 2218 – 2219).

Other effects

Statins appear to have favorable impact on psychological conditions. Elderly patients with coronary disease who take statins over the long term and show improvements in psychological disorders.

Statins are also considered therapeutically relevant in combination with other active substances such as, e.g., NSAIDs, COX-2 inhibitors etc. In one embodiment of the invention a suitable combination is with a statin and acetyl salicylic acid.

Other examples are:

Antiviral agents, for example:

Abacavir, Acyclovir, Famcyclovir, Nelfinavir, Valacyclovir, Trizivir, Descicloviir

Antidiabetic agents, for example:

Acarbose, Gliclazid, Insulin, Metformin, Tolbutamide

Cough suppressants and expectorants, for example:

Acetylcysteine, Dextromethorphan, Pentoxyverine, Bromhexine

Lipid regulating agents, for example:

Acipimox

Antidepressant agents, for example:

Amitriptyline, Imipramine, Bupropion, Efexor, Maprotiline, Moclobemide, Nefadozon, Reboxetine, Trimipramine, Lithiumcitrate, Paroxetine

Penicillin, for example:

Amoxicillin, Ampicillin, Flucoxacillin, Mecillinam, Phenoxymethylpenicillin, Pivampecillin

Spasmolytica, for example:

Baclofen, Flavoxat, Propanthelinbromide, Tizanidine

Agents for treatment of morbus menière, for example:

Betahistine

Antiparkinsonian agents, for example:

Biperiden, Orphenadrin, Pramipexol, Procyclidin, Ropinirol, Trihexylphenidyl, Bromocriptine

Laxatives, for example:

Bisacodyl

Anxiolytic sedatives, hypnotic and neuroleptic agents, for example:
Alprazolam, Bromazepam, Buspirone, Chlordiazepoxide, Lorazepam, Oxazepam, Diazepam, Clomethiazole

Glucocorticoides, for example:
Prednisolon, Budesonide

Diuretics, for example:
Bumetanide, Furosemide

Antihypertensive agents, for example:
Captopril, Diltiazem, Felodipine, Labetalol, Methyldopa, Metoprolol, Oxprenolol, Prazosin, Propranolol, Verapamil, Nifedipine, Isradipine, Pindolol, Clonidine

Antihypotensive agents, for example:
Midodrine, Desglymidodrine

Antiepileptic agents, for example:
Carbamazepine, Clonazepam, Clozabam, Gabapentine, Valproate

Antithyroid agents, for example:
Carbimazol

Muscle relaxant agents, for example:
Carisoprodol, Chloroxazone, Dantrolene

Antibacterial agents, for example:
Cephalexin, Cefuroxim

Anti-arrhythmic agents, for example:
Quinidine, Proprafenon

Antipsychotic agents, for example:
Chlorpromazine, Melperon, Pipamperon, Sulpirid, Thioridazine

Antihistamines, for example:

Cinnarizine, Cyclizine, Cyproheptadine, Dexchlorpheniramine, Metopimazine, Promethazine

GI-Motility stimulating agents, for example:
Cisapride, Domperidone

Antibiotics, for example:
Clarithromycin, Clindamycin, Erythromycin, Fusidic acid, Lymecycline, Tetracycline, Nitrofurantoin

Antimigraine agents, for example:
Clonidine, pizotifen, ergotamine, metoprolol, propranolol, timolol, tolfenamine acid, pizotifene, flunarizine, valproat, dihydroergotamine, naratriptan, almotriptan, eletriptan, sumatriptan, zolmitriptan, rizatriptan, combination of ASA and metoclopramide, clonidine

Opioid agonists, for example:
Codeine, Ketobemidone, Pentazocine, Pethidine, Tramadol

Analgesics and anti-inflammatory agents, for example:
Dichlorphenac, Fenoprofen, Ibuprofen, Indometacin, Ketoprofen, Lornoxicam, Naproxen, Tiaprofenic acid, Tolfenamic acid, Paracetamol, Acetylsalicylic acid, Ketorolac, Coffein and Fenazon combination, Codein and Paracetamol combination, Diflunisal

Anticoagulants, for example:
Dipyridamol

Anti-androgen agents, for example:
Flutamide

Anti-emetic agents, for example:
Metoclopramide, ondasetron, metoclopramide, ondasetron, haloperidol, chlorpromazine, fluphenazin, acepromazin, prochlorperazin, perphanazin, metopimazin, granisetron, tropisetron, cyclizin, promethazin, cinnarizin, chlorcyclizin, domperidon, decadron, prednisolon, prednison, methylprednisolon

Antimicrobial agents, for example:
Metronidazol, Trimethoprim

Anti-asthmatic agents, for example:
Pentoxifylline, Theophylline, Neophylline, Salbutamol, Ephedrine

Anti-alzheimer agents, for example:
Rivastigmin

Antigout agents, for example:
Probenecid

Calcium regulating agents, for example:
Calcitonin

Anti-angina agents, for example:
Trimetazidine, Nicorandil

Stimulating agents, for example:
Methylphenidate

Adrenerge alfa-receptor blocking agents, for example:
Tamsulosine

Anticholinergic agents, for example:
Tolferodine

Antimalaria agents, for example:
Quinine

Statins, for example:
Atorvastatin, cerivastatin (rivastatin), dalvastatin, lovastatin, fluvastatin, glenvastatin, pitavastatin (itavastatin, nisvastatin), pravastatin (eptastatin, epastatin), rosuvastatin, simvastatin (epistatin, synvinolin, velostatin) and tenivastatin
Other agents, for example:
Tagatose

Drugs used for treatment of diseases that have their peak symptoms in the early morning

For drugs with symptoms occurring in the late night/ early morning, such as for example arthritis and asthma, colon delivery are also an advantage as the formulation taken at bedtime will released the active substance in the late night/early morning hours, preventing the symptom peaks to occur.

The anti-arthritis agent Indomethacin is used as an example.

Indomethacin is a non-steroidal anti-inflammatory agent used in the symptomatic management of painful and inflammatory conditions. Indomethacin is readily absorbed from the GI-tract in adults and the peak plasma concentration is reached 2 hours after oral administration of a plain tablet. Indomethacin is about 99% bound to plasma proteins and the terminal elimination half-life range from 2,6 to 11,2 hours. The usual initial oral dose is 25 mg 2-3 times daily. To alleviate night pain and morning stiffness a CR formulation with colon delivery is ideal. Furthermore such a CR product can reduce the number of dosings during the day and thereby increase the patient compliance. Indomethacin is slightly soluble in water and soluble in ethanol.

Other agents are:
Anti-asthmatic agents, for example:
Pentoxifylline, Theophylline, Neophylline, Salbutamol

Anti-angina agents, for example:
Trimetazidine, Nicorandil

Anti-arthritis agents, for example:
Ibuprofen, Indomethacin, Flubiprofen, Diflunisal

Peptide or protein drugs where colon delivery could be interesting because of the expected lower proteolytic activity in the colon compared to the small intestine
Delivery of peptide or protein drugs to the colon might present an advantage due to the lower proteolytic activity in the colon compared to the small intestine.

Insulin is a pancreatic hormone involved in the regulation of blood glucose as well as having a role in the protein and lipid metabolism. When administered in an oral plain formulation Insulin has no hypoglycaemic effect as it is inactivated in the small intestine before absorption. It has been demonstrated that Insulin can be absorbed in the colon

and a colon specific delivery system might therefore represent a possibility to administer Insulin orally. The dose in each tablet with colon release properties is 50 IE Insulin.

Also colon delivery of the natural peptide Parathyroid hormone, PTH, involved in the regulation of the bone formation is interesting, as this administration form will increase the patient convenience/compliance compared to the injection formulations available at the time being. PTH can as a bone-building agent be used alone or in combination with other current available osteoporosis drugs, which primarily prevent further bone loss. In the following is given a description of PTH.

Fluoride, prostagladine E_2 (PGE_2) and parathyroid hormone (PTH) are compounds, which have been shown to stimulate an increase in bone mass in humans or experimental animals. While fluoride can lead to an increase in fracture rates and PGE_2 may have unwanted side-effects, the actions of PTH seem to be relatively specific for bone. PTH or its amino-terminal (1-34) fragment increases bone mass in osteoporotic humans, normal rats and dogs. PTH improves bone loss in oestrogen-depleted rats in both a bone losing phase and with established osteopenia (Morletet al. Curr Pharm Des 2001; 7:671-87).

Natural parathyroid hormone (PTH) is a polypeptide consisting of 84 amino acids synthesized and secreted by the parathyroid glands. PTH is a principal regulator of calcium homeostasis through actions on kidney, intestine and bone. In kidney, PTH acts on cells within the distal tubular portion of the nephron to enhance calcium re-absorption at cortical sites and to block sodium, phosphate and bicarbonate re-absorption in the proximal tubule. The hormone also stimulates cells of the proximal tubule to produce 1,25-dihydroxy vitamin D_3 by enhancing 1-hydroxylase activity. It is this potent vitamin D metabolite, which then promotes calcium uptake from the diet in the intestinal mucosa.

The direct responsiveness of different tissues and organs to PTH is mediated by cell surface membrane receptors that are linked to the intracellular production of cyclic adenosine monophosphate (cAMP) and diacylglycerol-like cells in bone and in kidney and vascular smooth muscle cells. These receptors respond to full-length PTH (1-84) or its amino terminal fragment, PTH (e.g. PTH 1-34 etc), but not to mid-region or carboxy-terminal fragments. Although a number of investigators have sought to ascribe a physiological role to the carboxy-terminal region of PTH, no consistent *in vivo* effects have been noted yet. It is believed therefore, that the biological responses to administration of PTH (1-84) is similar to those observed with the more intensively studied amino-terminal PTH (1-34) or (1-38).

In bone, the mechanism of action of the hormone is much more complex. The acute response to endogenous PTH secretion is the net liberation of calcium and this is also true during continuous PTH secretion to the hormone at pharmacological levels. When PTH or any of its N-terminal (e.g. PTH 1-34) fragments are administered at supraphysiological levels in a pulsatile (e.g. daily) fashion, however, the long-term effect is an up-regulation of bone formation that results in the net accumulation of newly mineralized bone tissue.

PTH can induce both bone resorption and bone formation and thus increase bone turnover. PTH usually exerts its action on bone to release calcium into the extracellular fluid as a process of bone remodelling and also to maintain the serum calcium concentration, but the exact mechanisms are not fully understood. In some circumstances PTH may exert actions on bone and can stimulate osteoblast proliferation and osteoblast function. The net effect of exogenous PTH administration on bone turnover depends on the pattern of PTH delivery; thus, a continuous infusion reduces bone volume whereas daily single injections result in a net increase. However, PTH may be administered by any suitable administration route.

In normal settings, 70-95% of circulating PTH is present as inactive C-terminal fragments. Intact PTH (1-84) constitutes only 5-30% of the circulating forms of the molecule. The biologically active N-terminal fragment is rapidly degraded *in situ* and there is little evidence that it is ever present in appreciable quantities in the circulation. Endogenous human PTH is rapidly metabolized primarily in the liver (60-70%) and kidney (20-30%).

Parathyroid hormone (PTH), especially intact human PTH (hPTH (1-84) and its various fragments hPTH (1-31), (1-34), (1-36), (1-38) and their modifications has been investigated for the use in the treatment of osteoporosis over the last 10 years. In the present context PTH encompasses PTH, PTH analogues, PTH derivatives and substances that have a PTH activity or related activity. It has been found that human parathyroid hormone fragments, in which the C-terminal amino acid is amino acid 35 to 38, preferably 37 or 38 and at least the first N-terminal amino acid has been removed, and analogs and derivatives thereof stimulate osteoblast activity and maximize bone formation without undesirable levels of bone resorption, antibody formation, or tachyphylaxis. The human parathyroid hormone fragments can be represented in accordance with standard nomenclature by the formula (m-n) PTH: (3-38PTH)-(28-38PTH), (3-37PTH) –28-37PTH), 2-35PTH-2-38PTH, and C-terminal amide derivative of the above mentioned where PTH

is human parathyroid hormone (hPTH) or a pharmaceutically acceptable salt or hydrolysable ester thereof.

Of the various kind of anabolic agents tested in the treatment of osteoporosis intermittent injections of PTH has proven to be the most effective up to date (Seeman E. et al. Trends Endocrinol Metab 2001; 12 (7): 281-3). However, other administration routes may also be efficient.

Although chronic continuous excess of PTH markedly increases bone resorption, as seen in the typical example of primary hyperparathyroidism and osteitis fibrosa generalisata, intermittent PTH administration has been found to stimulate bone formation in animals, providing a basis for the use of PTH as a therapeutic agent for osteoporosis. In addition to dramatically increasing trabecular bone density and also sustaining cortical bone density, PTH administration increases bone strength and reduces the fracture rate, e.g. 40 µg/daily (1-34 PTH) (Neer et al, N Engl J Med 2001,10;344(19):1434-41). Administration of PTH in combination with antiresorptive agents such as oestrogen, calcitonine, vitamin D and bisphoshonates augments its effect e.g. 50, 75 or 100 µg/daily (1-84 PTH) for one year follow by 10 mg alendronate daily for one year (Rittmaster RS et al. J Clin Endo Met 2000,85:2129-2134).

It is generally belived that all patients should always be supplemented with calcium and vitamin D, e.g. 1000-1500 mg calcium and 400-800 IU vitamin D.

Because of its bone anabolic action, PTH is expected to be effective for osteoporosis in those of advanced age with suppressed bone remodelling, which might not respond favourably to antiresorptive agents. (Fujita T, BioDrugs 2001;15(11):721-8).

In a specific embodiment of the invention the active substance contained in the composition is PTH, a fragment, an analog or a derivative thereof (in the present context the term PTH is used in a broad sense unless otherwise indicated, i.e. it includes fragments, analogs, derivatives, modifications such as PTH or fragments thereof wherein one or more amino acid has been substituted by other amino acids or wherein one or more amino acid has been modified or deleted). As appears from the following, a composition according to the invention may apart from PTH contain other active substances such as, e.g. calcium or calcium-containing compounds, vitamin D such as, e.g., vitamin D_3, or combinations thereof.

Other agents are, e.g.:

Hormones or hormone analogues, for example:

Desmopressin, Parathyroid hormone (PTH), Teriparatide acetate, Somastatin, Calcitonin, Insulin, Growth hormone

Also enzymes for example Phenylalanine ammonia-lyase (PAL), which is able to prevent phenylalanine from reaching the blood circulations in patients suffering from Phenylketonuria, are interesting in colon delivery.

Oral administration of PAL has to overcome two obstacles; first the acidic environment in the stomach and later the proteolytic enzymes present in the small intestine, these two obstacles can be overcomed by delivery of PAL specifically to the colon.

Other enzymes are, e.g. :

Humicola lanuginosa lipase, Hexoseaminidase, Streptokinase, Phenylalanine ammonia-lyase

Drugs, which are expected to be absorbed from a specific part of the small intestine (absorption window)

For drug with a narrow absorption window in the small intestine a precise delivery of the drug dose in this region of the small intestine might improve the absorption and oral bioavailability of the given drug substance.

An example of an active substance with an absorption window is calcium.

Calcium is used in the treatment and prevention of calcium deficiency as a result of malnutrition, decrease in parathyroid hormone activity and vitamin D deficiency. Furthermore calcium is used in the prevention and treatment of osteoporosis.

Calcium is absorbed actively in the duodenum and the jejunum and passively in the ileum; only 20-33% of the oral administered dose is absorbed. The dose of elementary calcium used in the prevention/treatment of osteoporosis is 1000-1500 mg daily.

By formulating a drug delivery system, which releases calcium at the absorption sites in the small intestine, the fraction of calcium absorbed might increase. In the following is given a more detailed description of calcium and a vitamin D such as, e.g., vitamin D_3.

In one aspect of the invention, a composition contains PTH optionally in combination with a calcium compound (such as one or more of those mentioned in the following) and/or a vitamin D compound (see below). Such a composition is designed to release the calcium compound in the stomach or in the intestine whereas the PTH first is released in the colon. The composition may furthermore contain a suitable amount of a vitamin D. In the latter case, the composition is designed so that vitamin D is release within the same period of time as that of the calcium compound. A specific embodiment appears in the examples herein.

Calcium

Function

Calcium is essential for a number of key functions in the body, both as ionized calcium and a calcium complex (Campell AK.Clin Sci 1987; 72:1-10). Cell behaviour and growth are regulated by calcium. In association with troponin, calcium controls muscle contraction and relaxation (Ebashi S. Proc R Soc Lond 1980; 207:259-86).

Calcium selected channels are a universal feature of the cell membrane and the electrical activity of nerve tissue and the discharge of neurosecretory granules are a function of the balance between intracellular and extra cellular calcium levels (Burgoyne RD. Biochim Biophys Acta 1984;779:201-16). The secretion of hormones and the activity of key enzymes and proteins are dependent on calcium. Finally calcium as a calcium phosphate complex confers rigidity and strength on the skeleton (Boskey AL. Springer, 1988:171-26). Because bone contains over 99% of the total body calcium, skeletal calcium also serves as the major long-term calcium reservoir.

Furthermore, calcium may have anticancer actions within the colon. Several preliminary studies have shown high calcium diets or intake of calcium supplementation is associated with reduced colon rectal cancer. There is increasing evidence that calcium in combination with acetylsalicylic acid (ASA) and other non-steroidal anti-inflammatory drugs (NSAIDS) reduce the risk the risk of colorectal cancer.

Recent research studies suggest that calcium might relieve premenstrual syndrome (PMS). Some researchers believe that disruptions in calcium regulation are an underlying factor in the development of PMS symptoms. In one study, half the women of a 466 person group of pre-menopausal women from across the U.S. were tracked for three menstrual cycles and were given 1200 mg of calcium supplements daily throughout the

cycle. The final results showed that 48% of the women who took placebo had PMS related symptoms. Only 30% of those receiving calcium tablet did.

Kinetics

The calcium content of the westernised diet is about 1 g/day. However, dietary calcium is present in only a few calcium-rich foods and the range in calcium intake, both within and between individuals is wide. In humans, absorption of calcium largely from the duodenum-jejunum is intermittent with meals. Calcium loss from the gut as endogenous secretions is passive and amounts to about 100 mg/day. On the other hand, calcium is absorbed by both active and passive mechanisms (Miller J. Z. et al. Am Inst Nutr 1990:265-74). On average, absorption in the young adult is only about 30% efficient. The main regulator of calcium absorption efficiency in humans is serum 1,25$(OH)_2$ vitamin D concentration, and although absorption efficiency increases as calcium intake decreases, it never achieves 100% efficiency. Once absorbed, the major flow of calcium is to bone and to kidney. In the kidney about 98% of the calcium that is filtered each day is reabsorbed, mainly under the regulation of parathyroid hormone (PTH) concentrations. The 2% un-reabsorbed calcium appears in urine as an obligatory calcium loss. In the bone of young adults, about 500 mg/day of calcium is deposited at the formation surfaces by osteoblasts and a similar amount released back to serum at the resorption surfaces by osteoclasts (Newton-John H et al. Clin Orthop 1970; 71:229-52). The overall result is that the skeleton remains in mineral balance. In older adults, however, age-related loss of bone occurs and there is a universal net loss of calcium from the skeleton. In children the rates of calcium transport are two to three times higher than the young adults, with formation greater than resorption such that there is net retention of calcium of about 300 mg/day and gain in bone (Wastney ME et al. Am J Physiol 1996; 271:208-16).

Gastric acidity assists in dissolving components of a standard meal. All calcium salts are more soluble in acidic media. Calcium carbonate and calcium phosphate are relatively water-insoluble and therefore clinical research support that calcium absorption from these salts is dependent on gastric acid production.

Homeostasis

In humans, the normal range of total calcium in serum is maintained at 8.8-10.2mg/100ml i.e. within about 15% of the mean concentration. About 40% of this calcium is bound to protein, 10% is complex bound with phosphate, sulphate and citrate and the remaining 50% is present as ionic calcium. The concentration of ionized calcium in serum is closely regulated through negative feedback of calcium on the secretion of PTH from the

parathyroid glands and the secretion of 1,25 $(OH)_2$ vitamin D from the kidney. In the parathyroid gland, the reduction of PTH secretion in response to a rise in serum calcium is dependant on the integrity of a calcium- sensing receptor. In the kidney, change in PTH-secretion is the major regulator of 1,25 $(OH)_2$ vitamin D production although serum calcium and serum phosphate also affect production. In addition, serum 1,25 $(OH)_2$ vitamin D also plays a major role in this homeostatic mechanism by regulating PTH secretion and its own production and catabolism.

Skeletal pathophysiology

In many animal models, chronic low calcium intake produces osteopenia. The osteopenia affects cancellous bone more than cortical bone and may not be completely reversible with calcium supplementation. If the animal is growing reduced calcium intake leads to stunting. In the premature human neonate the higher the calcium intake, the greater the intake, the greater the increase in skeletal calcium accretion which, if high enough, can equal gestational calcium retention. During growth chronic calcium deficiency causes rickets. Calcium supplements in both pre- and postpubertal healthy children leads to increased bone mass. In adolescents the higher the calcium intake, the greater the calcium retention, with the highest retention occurring just after menarche. Taken together, these data suggest that in children and adolescents considered to be taking an adequate intake of calcium, peak bone mass can be optimised by supplementing the diet with calcium. The mechanisms involved in optimising deposition of calcium in the skeleton during growth are unknown. They are probably innate properties of the mineralization process that ensures optimal calcification of the osteoid if calcium supplies are high. A high calcium intake does reduce PTH and bone turnover in children but the effect is small and unlikely to be the sole cause of increased calcium retention. The factors responsible for stunting of growth in states of calcium deficiency are also unknown but clearly involve growth factors regulating skeletal size.

In adults calcium supplementation reduces the rate of age-related bone loss (Dawson-Hughes B. Am J Clin Nut 1991;54:S274-80). Calcium supplements are important for individuals who cannot or will nor achieve optimal calcium intakes from food. Many different supplements including Bisglycino Calcium, Calcium Acetate, Calcium Carbonate, Calcium Chloride, Calcium Citrate, Calcium Citrate Malate, Calcium Cornate, Calcium Fluoride, Calcium Glubionate, Calcium Gluconate, Calcium Glycerophosphate, Calcium Hydrogen Phosphate, Calcium Hydroxyapatite, Calcium lactate, Calcium Lactobionate, Calcium Lactogluconate, Calcium Phosphate, Calcium Pidolate, Calcium Stearate and Tricalcium Phosphate (calcium acetate, bisglycino calcium, cornate, citrate, citrate malate,

glubionate, lactate, lactogluconate, and tricalcium phosphate) are available and can be used in a composition of the present invention. Other calcium sources may be water-soluble calcium salts, or complexes like e.g. calcium alginate, calcium-EDTA and the like or organic compounds containing calcium like e.g. calcium organophosphates. Use of bone meal, dolomite and other unrefined calcium sources is discouraged because these sources may contain lead and other toxic contaminants. However, such sources may be relevant if they are purified to a desired degree.

A review of 20 prospective calcium trials in postmenopausal women concludes that calcium supplementation on reduced bone loss is on average by about 1% year. In the elderly, calcium supplementation also reduces bone loss and the lower the prevailing dietary intake, the better the response in bone. The effect of calcium intake on the skeleton is to reduce the number of osteoporotic fractures, although this effect is not consistent across studies (Cumming RG et al. J Bone Miner Res 1997; 12:1321-9). The mechanism by which calcium supplementation slows bone loss is probably through a reduction in serum PTH. With age there is an increase in serum PTH and bone turnover due to the combined effects of reduced calcium intake and absorption and to vitamin D insufficiency. Calcium supplementation is most effective in this situation. Where PTH is already suppressed, such as in immobilisation and acute oestrogen deficiency, calcium supplementation is less likely to be so effective.

Vitamin D

Function

In addition to its action on calcium and skeletal homeostasis, vitamin D is involved in the regulation of several major systems in the body. The actions of vitamin D are medicated at the genome by a complex formed by 1,25-$(OH)_2$ vitamin D mainly produced in the kidney, with the vitamin D receptor (VDR). The latter is widely distributed in many cell types. The 1,25-$(OH)_2$ vitamin D/VDR complex has important regulatory roles in cell differentiation and in the immune system. Some of these actions are probably dependant on the ability of certain tissues other than the kidney to produce 1,25-$(OH)_2$ vitamin D locally and act as a paracrine (Adams JS et al. Endocrinology 1996;137:4514-7).

Metabolism

The major source of vitamin D is the skin where it is produced by the action of ultraviolet light on steroid precursors. Vitamin D, like calcium, is also present in a limited number of foods but although dietary sources can be important under circumstances of decreased sunlight exposure, vitamin D is not a true vitamin. It is a pro-steroid hormone that is

biologically inert until metabolized (Block G. Am J Epidemiol 1985; 122:13-26). In the liver, vitamin D is metabolized to 25-OH vitamin D, which functions as the major storage form by virtue of its long half-life due to high affinity for the vitamin D binding protein (DBP) in blood. In the kidney 25-OH vitamin D is further metabolized by a 1α-hydroxylase enzyme to 1,25-$(OH)_2$ vitamin D, the hormone responsible for the biological effects of vitamin D. The activity of the 1α-hydroxylase enzyme is tightly controlled by the blood levels of PTH, calcium and phosphate and by 1,25-$(OH)_2$ vitamin D itself. Because serum 1,25-$(OH)_2$ vitamin D has a much higher affinity for the VDR and a mush lower affinity for DBP than 25-OH vitamin D, 1,25-$(OH)_2$ vitamin D is responsible for the action of vitamin D except under circumstances of pharmacological concentrations of 25-OH vitamin D in serum. These occur with oral consumption of either vitamin D or 25-OH vitamin D and lead to vitamin D intoxication (Monkawa T et al. Bioche Biophy Res Commu 1997; 239;527-33).

Skeletal pathophysiology

In humans, deficiency of vitamin D results in rickets in children and osteomalacia in adults. The basic abnormality is a delay in the rate of mineralization off osteoid as it is laid down by the osteoblast (Peacock M. London Livingstone, 1993:83-118). It is not clear whether this delay is due to a failure of a 1,25-$(OH)_2$ vitamin D–dependant mechanism in the osteoblast or to reduced supplies of calcium and phosphate secondary to malabsorption or a combination of both. Accompanying the mineralization delay, there is reduced supply of calcium and phosphate, severe secondary hyperparathyroidism with hypocalcaemia and hypophosphatemia and increased bone turnover.

Vitamin D insufficiency, the preclinical phase of vitamin D deficiency, also causes a reduced calcium supply and secondary hyperparathyroidism, albeit of a milder degree than found with deficiency. If this state remains chronic, osteopenia results. The biochemical process underlying this state of calcium insufficiency is probably inappropriate levels of 1,25-$(OH)_2$ vitamin D due to a reduction in its substrate 25-OHD (Francis RM et al. Eur J Clin Invest 1983; 13:391-6). The state of vitamin D insufficiency is most commonly found in the elderly. With age there is a decrease in serum 25-OH vitamin D due to decreased sunlight exposure and possible to decreased skin synthesis. Furthermore, in the elderly the condition is exacerbated by a decrease in calcium intake and a paradoxical decrease in calcium absorption. The reduction in renal function with age giving rise to reduced renal 1,25-$(OH)_2$ vitamin D production may be a contributing factor. There are a number of studies of the effects of vitamin D supplementation on bone loss in the elderly. Some are without calcium supplementation and others are with calcium supplementation. It appears from the studies that although vitamin D supplementation is

necessary to reverse deficiency and insufficiency, it is even more important as far as the skeleton is concerned to provide calcium supplementation since the major skeletal defect is calcium deficiency. In literature based on clinical trials, recent findings suggest trends of need for higher doses of vitamin D for the elderly patients (Compston JE. BMJ 1998;317:1466-67). An open quasi-randomised study of annual injections of 150.000-300.000 IU of vitamin D (corresponding to approx. 400-800 IU/day) showed a significant reduction in overall fracture rate but not in the rate of hip fracture in treated patients (Heikinheimo RJ et al. Calcif Tissue Int 1992; 51:105-110). From a recently published trial was concluded that four monthly ~ four times/yearly supplementation with 100.000 IU oral vitamin D (corresponding to approx.800IU/day) may prevent fractures, however does not decrease PTH adequately, suggesting that a more frequent dose may be considered in future trials.

One aspect of vitamin intoxication is increased bone resorption. Both 25-OH vitamin D and 1,25-$(OH)_2$ vitamin D at high concentrations cause increased bone resorption *in vitro* and *in vivo* which can be blocked by antiresorptive agents such as estrogens and bisphoshonates (Gibbs et al. Postgrad Med J.1986;62:937-8). In the long term excess vitamin D leads to osteopenia (Adams et al. Annal Intern Med 1997:127; 203-6).

Recommended Daily Allowance (RDA) of calcium and vitamin D_3 (European Commission. Report on osteoporosis in the European Community. Action for prevention. Office for official Publications of the European Communities, Luxembourg 1998):

Group	Age (years)	Calcium (mg)*	Vitamin D_3 (µg)
Newborn	0-0.5	400	10-25
	0.5-1.0	360-400	10-25
Children	1.0-3.0	400-600	10
	4.0-7.0	450-600	0-10
	8.0-10	550-700	0-10
Men	11-17	900-1000	0-10
	18-24	900-1000	0-15
	25-65	700-800	0-10
	65+	700-800	10

Women	11-17	900-1000	0-15
	18-24	900-1000	0-10
	25-50	700-800	0-10
	51-65	800	0-10
	65+	700-800	10
Pregnant		700-900	10
Lactating		1200	10

* RDA of calcium varies from country to country and is being re-evaluated in many countries.

Other agents of interest are e.g:

Folic acid, Pravastatin, Ranithidine, Danazole, Vitamin B12, Calcium, Vitamin K

Combination of active substances with absorption window in the small intestine and active substances where delivery to the colon are an advantage:

Combinations of active substances in a drug delivery system according to the invention for treatment of a given indication might also be relevant. Such a combination could for example be a drug delivery system containing calcium aimed at the absorption window in the small intestine combined with colon delivery of PTH. Another relevant combination is a drug delivery system containing a vitamin D (e.g. D_3) aimed at the absorption window in duodenum and jejunum combined with colon delivery of PTH. A further relevant combination is a drug delivery system containing a calcium compound and vitamin D aimed at being released in the small intestine combined with PTH aimed at being released in colon.

The amount of the specific active substance in a drug delivery system according to the invention depends on the condition to be treated and on the age and condition of the patient. Moreover it depends on the frequency of the dosing, i.e. on the system is intended for use 1, 2, 3, 4, 5 or more times daily, weekly or monthly. A person skilled in the art will know how to decide the correct dosage in a drug delivery system of the invention.

In the case of a composition containing PTH, a person skilled in the art will know which dose to include in the composition based on clinical relevant data.

The same applies in the case of a composition containing PTH in combination with a calcium compound and/or a vitamin D.

The active substance may be present in any suitable layer of the unit of the drug delivery system according to the invention. In most cases, the active substance is present in a layer located between the inner core and the swellable layer, but it may also be present e.g. dispersed in the time controlled layer such as in a swellable layer.

Other additives

A drug delivery system according to the invention may further comprise one or more pharmaceutically acceptable excipients. The one or more pharmaceutically acceptable excipients may be present in any layer of the unit or added to the unit or units e.g. in order to enable compression of the units into e.g. tablets or in order to facilitate the manufacturing process and filling of the delivery system into a suitable dosage form (e.g. capsules, sachets etc.).

Suitable pharmaceutically acceptable excipients are selected from the group consisting of fillers, diluents, binders and sweeteners.

Specific examples include:
Agar, alginate e.g. sodium alginate, calcium bicarbonate, calcium carbonate, calcium hydrogen phosphate, calcium phosphate, calcium sulphate, carboxyalkylcellulose, cellulose, charged sodium polystyrene sulphonate resin, dextran, dextrates, dextrin, dibasic calcium phosphate (Emcompress), ethyl cellulose, gelatine, glucose, glyceryl palmitostearate, gummi arabicum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose, magnesium carbonate, magnesium chloride, magnesium oxide, maltodextrin, methylcellulose, microcrystalline cellulose, modified starches, polyethylene glycol, polyethylene oxide, polysaccharides e.g. dextran, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone/vinyl acetate copolymer, soy polysaccharide, sodium carbonate, sodium chloride, sodium phosphate, starch, dextrose, fructose, glycerin, glucose, isomalt, lactitol, lactose, maltitol, maltose, mannitol, aorbitol, sucrose, tagatose, trehalose, xylitol, alitame, aspartame, acesulfam potassium, cyclamic acid, cyclamate salt (e.g. calcium cyclamate, sodium cyclamate), neohesperidine dihydrochalcone, thaumatin, saccharin, saccharin salt (e.g. ammonium saccharin, calcium saccharin, potassium saccharin, sodium saccharin), sucralose and mixtures thereof.

One or more excipients may also be added in order to improve the stability, the taste, the storage time etc. of the composition (or the active substance(s) contained in the composition) or to improve the bioavailability of the active substance(s) including the dissolution rate, the absorption rate and the extent of absorption. To this end incorporation of an enhancer is suitable. In the following is given a number of examples on enhancers suitable for use in a composition of the present invention. Although the discussion is focused on peptides, the enhancers may suitably be used for any active substance for which an improvement in absorption is desired. Thus, the discussion below is not intended to limit the invention in any way. In those cases, where an enhancer is present in a composition of the invention, it can be incorporated in any of the layers contained in the composition. Normally, it is incorporated in the layer containing the active substance for which absorption should be enhanced or in a layer in close proximity to this.

The absorption of peptides and proteins in the gastro-intestinal (GI) tract is low, because the absorption depends on various important factors: the size, instability in the GI-tract etc. The peptides and proteins can be chemical deactivated by different proteases. The absorption may be improved by use of enzyme inhibitors, which may result in the deactivations of the enzymes (proteases). However, enzyme inhibitors might be absorbed and trigger several side effects including systemic toxicity. In general, low molecular weight absorption enhancers disrupt the mucosal layer of the gut tissue. There is therefore a risk that enhancement in absorption of peptides and proteins can be accompanied by toxic effects of such enhancers. Another way to improve the oral absorption is to increase the stability of peptides and proteins in the GI-tract by chemical modification.

It is therefore essential to ensure that, by opening tight junctions, the enzyme inhibitors and absorption enhancers are not absorbed together with the peptides or proteins.

Carrier systems are necessary to increase the residence time of the delivery system for a specific period of time or to delivery of the peptides or proteins at a desirable absorption site in the GI-tract, during which the peptides or proteins can be released and absorbed. These carrier systems should not essentially influence the physicochemical properties of the peptides or proteins.

Below are lists different types of substances that are suitable for use in a composition according to the invention in order to improve the absorption of one or more active

substances in particular of peptides and proteins either by inhibiting enzymes or enhancing the absorption of peptides and proteins.

Enzyme inhibitors, for example

Protease inhibitors (e.g. Aprotinin, Carboxyl Esterase, Carboxymethylcellulose-Bowman-Birk, Carboxymethylcellulose-Elastatinal, Chicken Ovomucoid, Chymostatin, Duck Ovomucoid, Lactate dehydrogenase, Leupeptin, Bestatin, α2-Macroglobulin, Soybean Trypsin)

Chelating agents (e.g. Ethylenediaminetetraacetic Acid (EDTA), Chitosan-EDTA, Chitosan-EDTA-Antipain, Chitosan-EDTA-Chymostatin, Chitosan-EDTA-Elastatinal, Chitosan-EDTA-Bowman-Birk inhibitor)

Various polymers (e.g. Carbomer, Chitosan, Chitosan-Antipain, Chitosan-Chymostatin, Chitosan-Elastatinal, Chitosan-DTPA (DTPA=DiethyleneTriaminePentaacetic Acid), Polycarbophil)

Of the above-mentioned enzyme inhibitors, Chitosan-EDTA, Chitosan-EDTA-Antipain, Chitosan-EDTA-Chymostatin, Chitosan-EDTA-Elastatinal, Chitosan-EDTA-Bowman-Birk inhibitor, Chitosan-Antipain, Chitosan-Chymostatin, Chitosan-Elastatinal, Chitosan-DTPA are especially suitable for use because enzymes inhibitors with low molecular weight such as Aprotinin or EDTA will be absorbed easily and may cause side effects as systemic toxicity. It is possible to avoid their systemic absorption and to exclude side effects (e.g. by covalent attach the enzyme inhibitors to unabsorbable hydrophilic matrices of high molecular weight or polymers with mucoadhesive properties (e.g. Chitosan)). Additionally, this approach may increase the luminal concentration and result in more effective inactivation of the enzymes.

Absorption enhancers

Ideally, appropriate absorption enhancers for use in a composition of the invention should have the following properties. A) Compatible with peptides and proteins with respects to possible chemical interaction, which might change the physicochemical structure and pharmacological activity of the peptides and proteins. B) Rapid response to open the tight junctions. C) Afford therapeutic levels of peptides or proteins in the systemic circulation. D) Rapid reversible effect to close the tight junctions in order to diminish probable side effects by avoiding the uptake of unwanted toxic substances in the intestine.

Fatty acids and surfactants increase the epithelial membrane permeability by interacting with the phospholipids bilayer of the intestinal membranes and may cause toxic side effects in the cells.

Fatty acids, fatty alcohols and fatty esters, for example:
Ethyl Oleate, Sodium Oleate, Lauric Acid, Methyl Laurate, Oleic Acid, Sodium Caprate

Surfactants, for example:
Dioctyl Calcium Sulfosuccinate, Dioctyl Potassium Sulfosuccinate, Dodecyltrimethylammonium Bromide, Glyceryl Monooleate, Hexadecyltrimethylammonium Bromide, Trimethyltetradecylammonium Bromide, Polyoxyehtylene Ethers (Polyoxyehtylene-9-lauryl Ether), Polysorbates, Sodium Dodecyl Sulphate, Sodium Dioctyl Sulfosuccinate, Sodium Laurate, Sodium Lauryl Sulfate, Sodium 5-methoxysalicylate, Sodium Salicylate, Sorbitan Esters

Selective absorption enhancers of a high molecular weight, such as anionic polyacrylates and cationic chitosans, may manage to selectively open the tight junctions. In addition to the ability of mucoadhesive substances to bind unspecifically to mucus, they may also increase paracellular permeability and inhibit the action of proteolytic enzymes. The increased paracellular permeability may allow not only the active substance but also toxic substances to be absorbed into the systemic circulation. Chitosan and its derivates (e.g. N-Trimethyl Chitosan Chloride) are known as potential absorption enhancers for peptides and proteins. They manage to selectively open the tight junctions to allow the passive absorption of peptides and proteins via the paracellular pathway. They display mucoadhesive properties and enhance the interaction of the delivery systems with the intestinal mucosa to prolong the duration of absorption.

Mucoadhesive polymers, for example:
Alginate, Cellulose derivates (e.g. Carboxymethylcellulose, Methylcellulose, Hydroyethyl Cellulose, Hydroxypropyl Cellulose, Hydroxypropyl Methylcellulose, Sodium Carboxymethylcellulose), Carbomer, Carbopol (Polyacrylic Acid), Carbopol-PEG, Chitin, Chitosan (α(1-4)2-amino 2 deoxy β-glucan), Trimethyl Chitosan, N-Trimethyl Chitosan Chloride, Poly(acrylamide), Polyacrylates (e.g. Poly(alkyl cyanoacrylate), Poly(butyl cyanoacrylate), Polyethylene Glycol, Polyethylene Oxide, Poly(ethyl cyanoacrylate), Poly(2-hydroxyethyl methacrylate), Poly(isobutyl cyanoacrylate) Poly(isohexyl cyanoacrylate), Poly(methyl methacrylate)), Poly(D,L-lactic acid), Poly-DL-Lactide-poly(ethylene glycol), Poly(lactic acid-co-glycolic acid), Polyanhydrides (e.g. Poly(fumaric

anhydride), poly(fumaric-co-sebacic anhydride)), Poly(vinyl alcohol), Polycarbophil, Polycarbophil-Cysteine, Poly(methylmethacrylate), Povidine-(polyvinylpyrrolidone), Starch (e.g. Amylose, Amylopectin), Sodium Hyaluronate, Hyaluronic acid, Thiolated polymers (Thiomers)). Of particular interest are Chitosans

Bile salts enhance the transmembrane transport of endogenous and exogenous lipophilic compounds as well as the paracellular transport of polar hydrophilic molecules across the intestinal epithelium.

Bile salts, for example:
Sodium Deoxycholate, Deoxycholic Acid, Sodium Cholate, Cholic Acid, Sodium Glycocholate, Sodium Glycodeoxycholate, Sodium Taurocholate, Sodium Taurodeoxycholate

Cytoadhesives bind specifically – via a receptor–ligand-like interaction – to the surface of the epithelial cells. They may transmit signals, which induce substrate-specific vesicular transport processes. From a toxicological point of view these specific transport processes may be preferred to the general increase of permeability offered by some mucoadhesives. Lectins are protein or glycoproteins of nonimmunological origin, which specifically recognise sugar molecules and therefore are capable of binding to glycosylated membrane components.

Cytoadhesives, for example:
Lectins (e.g. Lycopersicon Esculentum Agglutinin, Wheat Germ Agglutinin, Urtica Dioica Agglutinin).

A new family of low molecular weight carriers, derived from N-acylated amino acids, have been developed and are also useful in the present context. They are thought to increase selectively the mucosal uptake by inducing conformational changes in the peptide molecules. While forming non-covalent bonds with the carrier, the molecules undergo partial unfolding and may both relax their shape and expose inner lipophilic residues thus facilitating their transmembrane passage. Unlike traditional surfactants and detergents, this class of absorption enhancer has certain specificity for peptides and proteins and polyaminoglycans and is practically devoid of toxic activity toward the intestinal epithelial cells.

N-acylated Amino Acids (especially N-[8-(2-hydroxy-4-methoxy)bensoyl]amino Caprylic Acid (4-MOAC), 4-[4-(2-hydroxybenzoyl)amino]butyric Acid, Sodium N-[8-(2-hydroxybenzoyl)amino]-caprylate)

Various other suitable absorption enhancers are listed below.

Phospholipids, for example:
Hexadecylphosphocholine, Dimyristoylphosphatidylglycerol, Lysophosphatidylglycerol, Phosphatidylinositol, 1,2-Di(2,4-octadecadienoyl)-*sn*-glycerol-3-phosphorylcholine and Phosphatidylcholines (e.g. Didecanoyl-L-phosphatidylcholine, Dilauroylphosphatidylcholine, DipalmitoylPhosphatidylcholine, Distearoylphosphatidylcholine). Lysophosphatidylcholine is of particular interest.

Cyclodextrins, for example:
β-Cyclodextrin, Dimethyl-β-Cyclodextrin, γ-Cyclodextrin, Hydroxypropyl β-cyclodextrin, Methyl Cyclodextrin; especially Dimethyl-β-Cyclodextrin is of particular interest

Fusidic Acid derivatives, for example:
Sodium Taurodihydrofusidate, Sodium Glycodihydrofusidate, Sodium Phosphate-Dihydrofusidate; especially Sodium Taurodihydrofusidate is of particulare interest

Microspheres, for example:
Microspheres of Starch, Microspheres of Dextran, Micronspheres of Hyaluronic Acid Ester

Others:
Sodium salts of e.g. glycyrrhizic acid, capric acid, alkanes (e.g. azacycloalkanes), amines and amides (e.g. N-methyl-pyrrolidone, Azone), amino acids and modified amino acids compounds (e.g. acetyl-L-cysteine), polyols (e.g. propyleneglycol, hydrogels), sulfoxides (e.g. dimethylsulfoxide), terpenes (e.g. carvone), ammonium glycyrrizinate, hyluronic acid, isopropyl myristate, n-lauryl-beta-D-maltopyranoside, saponins, DL-octanonylcarnitine chloride, palmitoyl-DL-carnitine chloride, DL-stearoylcarnitine chloride, acylcarnitines, ethylenediaminedihydro-chloride, phosphate-dihydrofusidate, sodium CAP); especially n-lauryl-beta-D-maltopyranoside is of particular interest, alpha 1000 peptide, peptide MW<1000 comprising at least 6 mol% of aspartatic- and gGlutamic Acid, decomposed royal jelly, vitamin D_2, vitamin D_3, hydroxy-vitamin D_3, 1.25-dihydroxy-vitamin D_3, spirulina, proteoglycan, soyahydrolysate, lysin, lactic acid, di-fructose-anhydrid, vylitol Ca-(lactate),

hydrolyzate of casein in particular a caseinoglycomacropeptide, negative ionization of $CaCO_3$, acetylsalicylic acid, vitamin K, creatin.

Other specific embodiments of the invention

A drug delivery system according to the present invention may further comprise a second type of units comprising the same or a different active substance and the first and second types of units being designed to release the active substance(s) with different release rates. It may also comprise a third type of units comprising the same or a different active substance and the first, second and types of units being designed to release the active substance(s) with different release rates.

In a specific embodiment, the second and/or third type of units is designed to release the active substance in a controlled manner and/or, alternatively the second and/or third type of units is designed to release the active substance relatively fast from the system upon oral administration.

In another embodiment a drug delivery system according to the present invention comprises a mixture of units of the first, second and third types, wherein units of the first type are designed to release the active substance in the colon, units of the second type are designed to release the active substance in sustained manner and units of the third type are designed to release the active substance in a relatively fast manner upon oral administration.

The layer ii) may be contained in admixture with layer i), and the system may comprise a further therapeutically, prophylactically and/or diagnostically active substance.

In some cases the first type of units may also comprise a further active substance so as to obtain a so-called combination composition.

In a specific embodiment a drug delivery system according to the invention comprises as active substance midodrine and/or desglymidodrine of a pharmaceutically acceptable salt thereof. The system may be composed of one or more different types of units as described above in order to obtain a suitable dissolution pattern for the active substance and, accordingly, to be able to obtain a suitable plasma concentration in mammals such as humans after oral administration.

In those cases where a drug delivery system according to the invention contains midodrine and/or desglymidodrine and the system e.g. contains three different types of unit which each contains the active substance, but each type of unit has been designed to release the active substance in a specific manner (such as, e.g. the first type of units is designed to release the active substance in the colon, the second type of units is designed to release the active substance in a controlled manner, and the third type of units is designed to release the active substance almost immediately upon oral administration), the desired dissolution profile depends on a number of factors such as, e.g., the proportion of the total amount of the active substance that is present in each type of units. However, an overall dissolution profile should reflect a quick release follow by a relatively steady state, which again is followed by a quick release (corresponding to the release in colon) and then a decline. In such case, the individual profiles may vary within a broad range such as those described above. A person skilled in the art will be able to envisage other and more specific profiles suitable as a target for an individual active substance.

Accordingly, a suitable drug delivery system containing midodrine is a system, wherein the *in vitro* release is determined employing an *in vitro* dissolution method according to USP or Ph.Eur. and the *in vitro* release of midodrine and/or desglymidodrine calculated in percentage based on the declared content (% w/w) could be as exemplified in the following (in the present context the terms "at the most about" and "not more than about" are intended to have the same meaning):

Alternative 1

About 0.5 hours after start of the dissolution test at the most about 80% w/w is released,

About 3 hours after start of the dissolution test at least about 5% w/w is released, and/or

About 8 hours after start of the dissolution test at least about 50% w/w is released.

Alternative 2

About 0.5 hours after start of the dissolution test at the most about 70% w/w is released,

About 3 hours after start of the dissolution test at least about 10% w/w is released, and/or

About 8 hours after start of the dissolution test at least about 60% w/w is released.

Alternative 3

About 0.5 hours after start of the dissolution test at the most about 60% w/w is released,

About 3 hours after start of the dissolution test at least about 15% w/w is released, and/or

About 8 hours after start of the dissolution test at least about 70% w/w is released.

Alternative 4

About 0.5 hours after start of the dissolution test at the most about 60% w/w is released,

About 3 hours after start of the dissolution test at least about 20% w/w is released, and/or

About 8 hours after start of the dissolution test at least about 70% w/w is released.

Alternative 5

About 0.5 hours after start of the dissolution test at the most about 60% w/w is released,

About 4 hours after start of the dissolution test at least about 15% w/w is released, and/or

About 7 hours after start of the dissolution test at least about 60% w/w is released.

Alternative 6

About 0.5 hours after start of the dissolution test at the most about 60% w/w is released,

About 4 hours after start of the dissolution test at least about 10% w/w and/or at the most about 90% w/w is released, and/or

About 7 hours after start of the dissolution test at least about 70% w/w is released.

Alternative 7

About 0.5 hours after start of the dissolution test at the most about 60% w/w is released,

About 4 hours after start of the dissolution test at least about 20% w/w and/or at the most about 90% w/w is released, and/or

About 7 hours after start of the dissolution test at least about 70% w/w is released.

Alternative 8

About 0.5 hours after start of the dissolution test at the most about 50% w/w is released,

About 4 hours after start of the dissolution test at least about 30% w/w w/w is released, and/or

About 7 hours after start of the dissolution test at least about 75% w/w is released.

Alternative 9

About 0.5 hours after start of the dissolution test at the most about 50% w/w and/or at least about 10% w/w is released,

About 4 hours after start of the dissolution test at least about 40% w/w w/w and/or at the most about 90% is released, and/or

About 7 hours after start of the dissolution test at least about 80% w/w is released.

Alternative 10

About 0.5 hours after start of the dissolution test at the most about 45% w/w and/or at least about 15% w/w is released,

About 4 hours after start of the dissolution test at least about 45% w/w w/w and/or at the most about 80% is released, and/or

About 7 hours after start of the dissolution test at least about 85% w/w is released.

Alternative 11

About 0.5 hours after start of the dissolution test at the most about 50% w/w is released,

About 5 hours after start of the dissolution test at least about 20% w/w such as, e.g., at least about 30% w/w or at least about 50% w/w is released, and/or

About 6 hours after start of the dissolution test at least about 50% w/w such as, e.g., at least about 60% w/w, at least about 70% w/w, at least about 80% w/w or at least about 85% w/w is released.

Other suitable dissolution profiles are:

Time (hours)	range (% w/w of declared content)
0.5	5-80
3	10-95
5	20-100

Time (hours)	range (% w/w of declared content)
0.5	10-70
3	10-95
5	20-100

Time (hours)	range (% w/w of declared content)
0.5	5-60
3	10-95
5	20-100

Time (hours)	range (% w/w of declared content)
0.5	5-50
3	10-95
5	20-100

Time (hours)	range (% w/w of declared content)
0.5	5-80
3	20-90
5	20-100

Time (hours)	range (% w/w of declared content)
0.5	5-80
3	25-85
5	20-100

Time (hours)	range (% w/w of declared content)
0.5	5-80
3	30-80
5	20-100

Time (hours)	range (% w/w of declared content)
0.5	5-80
3	30-70
5	20-100

Time (hours)	range (% w/w of declared content)
0.5	10-50
3	30-70
5	40-80

Time (hours)	range (% w/w of declared content)
0.5	20-40
3	40-65
5	50-75

or any combination thereof

The following table may be read as individual points on a dissolution profile or in any combination. Accordingly, a drug delivery system containing midodrine and/or desglymidodrine may fulfil one or more of the following requirement for each pair of (time, %)

Time (hours)	range (% w/w of declared content)
0.5	20-40 (or 5-70)
1	26-46 (or 10-70)
3	41-61 (or 15-80)
4	46-66 (or at least 20)

5	51-71 (or at least 30)
6	at least 50 (or at least 60, 70, 80 or 90)

With respect to release of PTH from a composition comprising PTH as an active substance (optionally together with calcium and/or vitamin D), the dissolution profile would suitable fulfil the following: a lag time of about 2 hours (not more than 10% w/w of the active substance is released within this period when tested in 0.1 N HCl) followed by a further lag time of about 2-4 hours and then a release period where 60% w/w or more such as, e.g., 70% w/w or more, 75% w/w or more, 80% w/w or more, 85% w/w or more, 90% w/w or more, 95% w/w or more, 98% w/w or more of the total amount of active substance contained in the composition is released. The release period typically last for from about 5 min to about 8 hours such as from about 10 min to about 7 hours, from about 20 min to about 6.5 hours, from about 30 min to about 6 hours, from about 30 min to about 5.5 hours, from about 30 min to about 5 hours, from about 30 min to about 4.5 hours or from about 30 min to about 4 hours.

The dissolution of calcium and/or vitamin D may be relatively fast. Thus, at least 50% w/w such as, e.g. at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w or at least 95% w/w should be released within 15 min.

Preparation of a drug delivery system according to the invention

A drug delivery system according to the invention may be prepared by use of any convenient method. A suitable method used by the present for the preparation of a composition according to the invention is described in the following. The method is especially designed to avoid problems with respect to static electricity that leads to adherence of the particulate material to the coating equipment and/or other particles. Furthermore, such problems may lead to poor reproducibility, poor yield and/or insufficient and/or uneven coating. The method suitable for use in the present context also takes into account that the particulate matter must not be overwetted. Both situations (i.e. static electricity and overwetting) lead to unwanted agglomeration of the particulate material.

The coating is performed in coating equipment, which comprises a coating chamber having

i) means for supply of a coating composition, and
ii) means for supply of inlet air to provide a flow of inlet air,

the method comprises

i) loading uncoated particulate material into the coating chamber,

ii) providing a flow of inlet air that has been adjusted so that the humidity of the inlet air ensures that unwanted agglomeration of the particulate material and/or adherence to the coating equipment are substantially reduced or avoided during the coating process, and

iii) spraying on the particulate material a coating composition comprising a solvent that contains at least about 70 % v/v of one or more organic solvents and at the most about 30% v/v of an aqueous medium,

to obtain coated particulate material containing at the most about 20% w/w (determined as described herein).

In general the coating process can be performed in any suitable coating equipment such as, e.g., a fluid bed (e.g. top spray, bottom spray, tangential spray), a spray dryer (e.g. co-current, counter-current) or a side-vented coating pan.

In general, coating with an organic solvent based composition leads to a stronger film than when water based coating composition is used. By using the present method it is possible to avoid undesired agglomeration of particles during the coating process, which is a clear advantage form a process economical point of view.

When coating particulate material like e.g. pellets it is the objective to supply each pellet with a uniform layer of film giving a well-defined and controllable release of the active substance. Therefore, agglomeration of pellets or adherence of pellets to the walls of the coating equipment may make it impossible to meet predetermined requirements such as, e.g., dissolution requirements, yields, particle size etc.

An example of such a material is cellulose spheres, which revealed many problems when subject to organic based coating. In general agglomeration or adherence will occur if the coating process is carried out under too wet conditions with a too high liquid flow rate. However, when dealing with an organic based coating process agglomeration and/or adherence can also occur caused by static electricity. Static electricity will occur if the relative humidity in the process air flow is too low. Reducing the problem with the static electricity can be solved by e.g. increasing the process air flow with the purpose of making the coating process more vigorous or by making the process more wet by increasing the liquid flow rate. However, neither of these suggestions was optimal in the present case.

Sometimes, problems relating to static electricity may be overcome by using different approaches such as, e.g. addition of an increased amount of talc or other similar agents, reduction of the polymer content in the coating composition, decreasing the viscosity of the coating composition and/or use different solvent systems having a higher evaporation rate (e.g. acetone). All these different approaches are investigated and the only one that seems to solve some of the problems is to lower the polymer concentration. However, it is not optimal as it generally lead to too long coating times (more than about 7 hours) and more solvent is needed, which lead to an uneconomical process and waste problems.

Accordingly, other alternative solutions are necessary in order to solve the problem with unwanted agglomeration. The inventors have found that when the inlet air carried an amount of water in a certain interval, this leads to a specific range of relative humidity in the coating chamber. Keeping the relative humidity within such a critical range turned up to lead to the desired result by which the static electricity of the particulate material is eliminated or significantly reduced and at the same time the relative humidity has a level that does not lead to overwetting of the particulate material.

In other words, a solution to the problem is achieved by increasing the relative humidity, RH, in the coating chamber by adjusting the amount of water in the inlet air. However, the level of RH in the coating chamber is very critical and the right level cannot be predicted easily. Too low RH will not eliminate the static electricity and too high RH will damage the film formation and may furthermore lead to agglomeration of the pellets.

In a specific embodiment of a method suitable for use for the preparation of a system according to the invention, the concentration of oversized agglomerates is normally at the most about 18% w/w such as, e.g., at the most about 15% w/w, at the most about 13% w/w, at the most about 10% w/w, at the most about 9% w/w, at the most about 8% w/w, at the most about 7% w/w, at the most about 6% w/w, at the most about 5% w/w, at the most about 4% w/w, at the most about 3% w/w or at the most about 2% w/w based on the total weight of the coated particulate material.

As mentioned above, the humidity of the inlet air in a method of the invention must be adjusted to a range that results in coated particulate material, wherein the percentage of oversized agglomerates is at the most 20% w/w such as, e.g., at the most about 18% w/w such as, e.g., at the most about 15% w/w, at the most about 13% w/w, at the most about 10% w/w, at the most about 9%, w/w at the most about 8% w/w, at the most about 7% w/w, at the most about 6% w/w, at the most about 5% w/w, at the most about 4% w/w, at

the most about 3% w/w or at the most about 2% w/w based on the total weight of the coated particulate material.

The above-mentioned range may suitably be determined by subjecting samples of the uncoated particulate material to a test, which involves coating the particulate material under conditions that involve changing the humidity of the inlet air and determining the percentage of oversized particulate material for each humidity level.

In specific embodiments, the uncoated particulate material contains at the most about 15% w/w of water such as at the most about 10% w/w such as, e.g., at the most about 7.5% w/w, at the most about 7% w/w, at the most about 6% w/w, at the most about 5.5% w/w such as about 5% w/w.

Examples of such a particulate material is e.g. cellulose spheres. In a specific embodiment, such cellulose spheres have a density of about 1.5 g/cm^3.

Alternatively, the content of water in the particulate material is at the most about 5% w/w such as, e.g., at the most about 4.5% w/w, at the most about 4% w/w, at the most about 3.5% w/w, at the most about 3% w/w, at the most about 2.5% w/w such as about 2% w/w or 1% w/w. A suitable example is e.g. sucrose spheres.

During the coating process the water content of the particulate material may be reduced during the coating process. This is for example observed when cellulose spheres are coated with a method of the invention. The reduction in water content may be at least about 25% w/w such as, e.g., at least about 30% w/w, at least about 40% w/w, at least about 50% w/w, at least about 60% w/w, at least about 70% w/w or at least about 75% w/w.

In a specific embodiment, the particulate material may be essentially water insoluble such as, e.g., cellulose spheres, or it may essentially water soluble such as, e.g., sucrose spheres.

Solvents suitable for use in the coating process

The coating composition suitable for use is based on an organic solvent selected from the group consisting of:

Acetone, chloroform, dichoromethane, ethanol, ether, hexane, isopropanol, methanol, methyl acetate, methyl isobutyl ketone, methylene chloride, n-butanol, n-propanol, toluene, water, xylen, and mixtures thereof.

In general ethanol, isopropanol and the like are preferred (if the process conditions makes it possible) as they are normally regarded as less harmless organic solvents.

Normally, the coating composition comprises at least about 70% v/v such as, e.g., at least about 85% v/v, at least about 90% v/v, at least about 95% v/v, at least about 97% v/v, at least about 99% v/v such as about 100% v/v of an organic solvent.

The solvent of the coating composition may in certain cases contain up to about 30% v/v water or aqueous media. Normally water is not present in the solvent or only in concentrations below 25% v/v such as, e.g., at the most about 20% v/v, at the most about 15% v/v, at the most about 10% v/v, at the most about 5% or at the most about 2.5% v/v.

The coating composition may also comprise a mixture of solvents selected from the group consisting of (all % in vol/vol):
20% ethanol, 80 % toluene
5 % ethanol, 95 % toluene
80% ethanol, 20 % methylene chloride
50% ethanol, 50% methylene chloride
20% ethanol, 80 % methylene chloride
70 % acetone, 30 % n-propanol
65% acetone, 35 % isopropanol
50% acetone, 50% Dowanol (Dow) PM glycol ether
14 % methanol, 86 % methylene chloride
80 % methyl acetate, 20 % n propanol
85% methyl acetate, 15 % methanol
65% methyl acetate, 35% Dowanol (Dow) PM glycol ether
70% Methyl isobutyl ketone, 30% methanol, and
65% methyl isobutyl ketone, 35% ethanol.

Coating conditions etc.

As mentioned above, a very critical parameter is the relative humidity. The relative humidity in the coating chamber during coating is from about 20 to about 60% such as, e.g., from about 25% to about 55% such as, e.g., from about 25% to about 50%, from

about 25% to about 45%, from about 30% to about 45%, from about 35% to about 50% or from about 25% to about 35%. Normally, a suitable relative humidity should be determined with a view to the product temperature. With respect to the mentioned relative humidity, the temperature of the particulate material during coating is normally kept at a temperature in a range from about 20 to about 60 °C such as, e.g., about 20 to about 50 °C, from about 25 to about 45 °C, from about 27 to about 40 °C or from about 27 to about 35 °C.

Furthermore, it has been observed that it is of an advantage to keep the temperature difference between the temperature of the particulate material in the coating chamber and the temperature of the inlet air during coating relatively small. Thus, the temperature difference is normally at the most about 15 °C such as, e.g., at the most about 12 °C, at the most about 11 °C, at the most about 10 °C, at the most about 9 °C, at the most about 8 °C, at the most about 7 °C, at the most about 6 °C or at the most about 5 °C.

In order to obtain a suitable relative humidity in the coating chamber the inlet air is adjusted to predetermined water content taken into consideration the temperature of the particulate material in the coating chamber.

In general, the water content of the inlet air expressed as the dew point of the inlet air is at the most about 20 °C such as, e.g., at the most about 18 °C, at the most about 17 °C or at the most about 16°C and/or the dew point of the inlet air is at least about 7 °C such as, e.g., at least about 8 °C.

In a specific embodiment, the temperature of the particulate material during coating is from about 26 to about 32 °C, the dew point of the inlet air is from about 12 to about 14 °C and the relative humidity of the coating chamber is from about 28% to about 47%.

In another embodiment, the temperature of the particulate material during coating is from about 26 to about 32 °C, the dew point of the inlet air is from about 14 to about 17 °C and the relative humidity of the coating chamber is from about 34% to about 50%.

In a further embodiment, the temperature of the particulate material during coating is from about 26 to about 32 °C, the dew point of the inlet air is from about 7 to about 12 °C and the relative humidity of the coating chamber is from about 23% to about 35%.

Coating compositions

The coating composition comprises a polymer such as a film-forming polymer. The coating may be a modified release coating, an immediate release coating, a taste-masking coating, an enteric coating etc.

Suitably a film coating normally comprises a water insoluble polymer selected from the group consisting of:
Ammonio methacrylate copolymer (Eudragit RL, Eudragit RS), cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose butyrate, cellulose propionate, cellulose valerate, crospovidone, ethyl cellulose, hydroxypropylcellulose, hydroxypropyl methyl cellulose (HPMC), hydroxyethylcellulose, polyacrylate dispersion (Eudragit NE), polydiethylaminomethylstyrene, polymethylstyrene, polyvinyl acetate, polyvinyl formal, polyvinyl butyryl, wax, and mixtures thereof.

An enteric coating may contain an enteric polymer. Suitable enteric polymers are selected from the group consisting of:
Amylose acetate phthalate, cellulose acetate phthalate CAP (pH cut off about 6.2), cellulose acetate succinate, cellulose acetate trimellitate CAT (pH cut off about pH 5.0), carboxymethyl ethylcellulose, formalin treated gelatine, hydroxypropyl methylcellulose acetate succinate HPMCAS (pH cut off about 5.0-5.5), hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose phthalate HPMC-P (pH cut off about 5.0 and about 5.5), methacrylic acid copolymer (Eudragit L) (pH cut off about 5.5 and about 6), methacrylic acid copolymer (Eudragit S) (pH cut off about 7), methacrylic acid copolymer (Eudragit FS) (pH cut off about 7.5), polyvinyl acetate phthalate PVAP (sureteric), shellac, starch acetate phthalate, styrene-Maleic acid copolymer, zein, and mixtures thereof.

The coating composition may further contain one or more additives such as, e.g., a plasticizer, an antiadherence agent (e.g. PEG, talc, aerosil etc.), a taste-masking agent (flavour, color, aroma etc.), an enhancer etc.

Other aspects of the invention

The invention also relates to a method for administering active substance to the colon, the method comprising administering to a patient a sufficient amount of a drug delivery system according to the invention. In a further aspect the invention relates to a drug delivery system comprising midodrine and/or desglymidodrine for delivering the active substance to the colon. Such a delivery system is typically designed so that it enables a relatively fast release, followed by a period with a relatively constant release and then a

second period with a fast release, namely when the delivery system reaches the colon. The particulars and details given above under the main aspect of the invention applies *mutatis mutandis* to these further aspects.

Legends to figure

Figure 1 shows schematically a first unit for use according to the invention. The unit comprises an inner core (in this example the core is cellulose sphere) surrounded by a layer containing the active substance. On top on this layer is the time controlled layer (here it is a swelling layer) that is coated with a water insoluble membrane. Finally, an enteric membrane is added.

In general, the layer containing the active substance constitute from about 0.5 to about 90% w/w such as, e.g., from about 1% w/w to about 80% w/w, from about 1.5% w/w to about 70% w/w, from about 2% w/w to about 60% w/w, from about 2% w/w to about 50% w/w of the first unit.

The time controlled layer normally constitutes from about 10% w/w to about 90% w/w such as, e.g., from about 20% w/w to about 90% w/w, from about 30% w/w to about 85% w/w of the first unit.

The water insoluble membrane normally constitutes from about 4% w/w to about 25% w/w of the first unit and the enteric membrane normally constitutes from about 2% w/w to about 25% w/w of the first unit.

MATERIALS AND METHODS

***In vitro* dissolution test method**

Apparatus	Ph.Eur./USP dissolution apparatus
Dissolution medium 1 (0 to 2 hours)	acidic stage (up to pH 4.0)
Dissolution medium 2 (2 to 10 hours)	buffer stage (pH 5.0 to 8.0
Time for medium change	2 hours
Media Temperature	37°C ± 0.5°C
Agitation/flow rate/dip per minute	established by evaluating the specific formulation to be tested.
Detection system	established by evaluating the specific formulation to be tested

A number of units/capsules/tablets are tested. The test result is calculated by the use of a reference standard of the active substance. The test result is reported as the average of three or more - determinations.

A person skilled in the art is capable of defining appropriate testing method conditions for the specific pharmaceutical formulations described in present document.

Method for quantification of degree of agglomeration

The following method is used to determine the degree of agglomeration.

- A representative sample is drawn from the coated product.
- The sample is by use of a standard sieve analysis equipment divided into fractions of a size of approx. 100 µm.
- These fractions are inspected with the purpose of determining the amount of agglomerates within each fraction. Agglomerates are defined as lumps consisting of two or more units of the original particulate material sticking together. The inspection is to be started with the fraction containing the smallest particles and can be done either visually followed by quantification based on weighing or by microscopy optionally combined with image analysis followed by quantification based on calculation of the volume of the equivalent spheres of the particles/agglomerates. The optimal choice of method for quantification depends on whether the use of microscopy has been appropriate.
- The first fraction that has a content of more that 90% of agglomerates is identified.
- The smaller screen size used to identify this fraction is used for dividing the whole batch of coated particulate material into two groups: good material and agglomerates.
- These two groups of material are weighed and the amount of agglomerates in % (w/w) of the total amount of material is calculated.

EXAMPLES

Some of the examples herein illustrate units that have a 5 layer spherical structure, which contains a core, drug, swelling agent, water insoluble membrane and enteric membrane. After the system is administered via the oral route the enteric membrane prevents water from entering into the system as long as the system is in the stomach. When the system enters into a more alkaline environment the enteric membrane quickly dissolves and the

pre-programmed lag time starts. The water penetrates through the insoluble but permeable membrane and starts hydrating the swelling agent. When stress by expansion of the hydrated swelling agent exceeds the tensile strength of the water insoluble membrane the disruption of the membrane occurs. Finally, the drug release is initiated (see figure 1). Drug release is triggered by membrane destruction and the time until the destruction creates the lag time for the release. The lag time can be controlled by the composition and/or thickness of the swelling agent and the water insoluble membrane but prolonging the lag time initiates larger variation on the lag time and decrease the release rate.

Example 1

Preparation of cores with a Midodrine containing layer

2 kg Cellulose Spheres with a particle size between 350-500µm or between 500-700 µm were coated with a Midodrine containing coat and an outer coat in a Glatt GPCG fluid-bed equipped with a rotary processor. The nozzle was placed in the lowest position. The distance from the wall to the nozzle point was 25 mm and the nozzle port size was 1.2 mm. The spray pressure was 2.5 bar and the rotations rate on the disk was 500 rpm. The product differential pressure was approximately 1.5 kPa.

The composition of the Midodrine coat (18.6% w/w dry matter) and outer coat (8% w/w dry matter) are shown in table 1 and 2.

Table 1

Ingredients	Amount (g)
Midodrine hydrochloride	172.5
Hydroxypropyl methylcellulose E5	63.9
Talc	42.6
Purified water	1221.0
Total	1500.0

Table 2

Ingredients	Amount (g)
Hydroxypropyl methylcellulose E5	40.0
Talc	40.0
Purified water	920.0
Total	1000.0

In the coating process 11.7% w/w Midodrine coat and 1% w/w outer coat were applied. The amount of dry matter applied is calculated in percentage of the core weight.

The Cellulose Spheres were heated to 40 °C and throughout the coating process the product temperature was kept at approximately 36 °C by adjustment of the liquid flow rate in the interval from 10 to 20 g/min. The inlet air temperature and the process airflow were kept at approximately 50 °C and 100 m^3/h, respectively. The inlet air was dehumidified leading to a dew point of less than -15 °C. After the application of the coatings the coated Cellulose Spheres were dried for 15 minutes with an inlet air temperature at 55 °C and a rotations rate on the disk at 350 rpm.

After coating, the coated Cellulose Spheres were screened through a screen size that was approximately 50% larger than the original largest particle size. Oversized material: less than 1%. The content of Midodrine was at least 98% w/w.

Example 2

Preparation of controlled release cores

2 kg cores as obtained from Example 1 with a particle size between 500-700 µm were coated with a diffusion coat and an outer coat in a Glatt GPCG fluid-bed equipped with a rotary processor. The composition of the diffusion coat (15.1% w/w dry matter) is shown in table 3. The outer coat composition of Example 1 was used.

Table 3

Ingredients	Amount (g)
Hydroxypropyl methylcellulose E5	9.83
Magnesium stearate	2.02
Talc	19.65
Eudragit NE30D	648.00
Purified water	820.50
Total	1500.00

In the coating process 7% w/w diffusion coat and 1% w/w outer coat were applied.

The cores were coated as described in Example 1 with the exception that the cores were heated to 30 °C throughout the coating process the product temperature was kept at

approximately 25 °C by adjustment of the liquid flow rate in the interval from 10 to 20 g/min. The inlet air temperature and the process airflow were kept at approximately 45 °C and 100 m^3/h, respectively. The coated cores were cured at a product temperature of approximately 70 °C for 60 minutes and thereafter cooled to a product temperature below 35 °C. Screened through a 1000 µm screen. Oversized material: <5% w/w.

Example 3

Preparation of cores with a swelling layer using suspension coating

1 kg cores as obtained from Example 1 with a particle size between 350-500 µm were coated with a swelling agent and an outer coat in a Glatt GPCG fluid-bed equipped with a rotary processor. The composition of the suspension coat (25% w/w dry matter) and the outer coat (4.2% w/w dry matter) are shown in table 4 and 5.

Table 4

Ingredients	Amount (g)
L-HPC LH-31	4472
Hydroxypropyl cellulose L-/fine	903
Ethanol 99.9%	16125
Total	21500

Table 5

Ingredients	Amount (g)
Hydroxypropyl cellulose L-/fine	63.0
Ethanol 99.9%	1437.0
Total	1500.0

In the coating process 400% w/w L-HPC and 1% w/w outer coat were applied.

The cores were coated as described in Example 1 with the exception that the inlet air was humidified. The dew point was in the interval from 11 to 12 °C. The cores were heated to 25 °C and throughout the coating process the product temperature was kept at approximately 15 °C by adjustment of the liquid flow rate in the interval from 35 to 45 g/min. The inlet air temperature and the process airflow were kept at approximately 25 °C and 100 m^3/h, respectively. The coated cores were dried on trays for approximately 24

hours at 40 °C. The dried cores were fractionated by screening through a lower screen of 710 µm and an upper screen of 1000 µm.

Example 4

Preparation of cores with an aim of obtaining a 3 hours lag time

2 kg of cores as obtained from Example 3 were coated with a water insoluble coat in a Glatt GPCG 3 fluid-bed equipped with a rotary processor. The composition of the water insoluble coat (10.9% w/w dry matter) is shown in table 6.

Table 6

Ingredients	Amount (g)
Ethyl cellulose 20	563.0
Polyethylene glycol 6000	197.0
Colloidal silica dioxide	113.0
Ethanol 99.9%	7127.0
Total	8000.0

In the coating process 42.2 % w/w water insoluble coat was applied.

The cores were coated as described in Example 3 with the exception that the dew point was in the interval from 10 to 11 °C. The cores were heated to 30 °C and throughout the coating process the product temperature was maintained substantially in the interval from 28 to 31 °C by adjustment of the liquid flow rate in the interval from 10 to 20 g/min. The inlet air temperature and the process airflow were kept at approximately 35 °C and 100 m^3/h, respectively. The coated cores were dried for 15 minutes. The coated cores were screened through a 1200 µm screen. Oversized material: <5% w/w.

Example 5

Preparation of cores for colon delivery

2 kg of cores as obtained from Example 4 were coated with an enteric coat in a Glatt GPCG 3 fluid-bed equipped with a rotary processor. The composition of the enteric coat (7.5% w/w dry matter) is shown in table 7.

Table 7

Ingredients	Amount (g)
Hydroxypropyl methylcellulose phthalate	480.0
Triethyl citrate	24.0
Colloidal silica dioxide	96.0
Purified water	1110.0
Ethanol 99.9%	6290.0
Total	8000.0

In the coating process 29% w/w enteric coat was applied.

The cores were coated as described in Example 4 with the exception that the dew point was in the interval from 14.5 to 15.8 °C. The coated cores were screened through a 1200 µm screen. Oversized material: <5% w/w.

Example 6

Preparation of a Midodrine modified release composition made in the form of capsules containing multiple units

A Midodrine modified release product was prepared by manufacturing one type of cores with a Midodrine containing layer, which afterwards was coated with different types of film coatings. The capsule ends up with 3 different types of cores: a) non-coated cores except for the active substance (Example 1), b) diffusion coated cores (Example 2) and c) cores for colon delivery (Example 5).

The 3 different cores were filled into hard gelatine capsules step by step with capsule filling machine having 3 fill units. The amount of cores per capsule is shown in table 8.

Table 8

Unit	% midodrine per core type in a capsule
Cores type 1	25
Cores type 2	38
Cores type 3	37
Total	100

Example 7

Preparation of cores containing Levamisole

The present example illustrates the preparation of cores containing Levamisole, as an alternative to cores with a drug containing layer.

The cores were prepared by the use of the extrusion/spheronization technique. The composition of the cores is shown in table 9.

Table 9

Ingredients	Amount (g)
Levamisole hydrochloride	250.0
Microcrystalline cellulose	563.0
Lactose monohydrate	1637.0
Sodium carboxymethylcellulose	50.0
Purified water	775 g

The ingredients were mixed and wetted in a Fielder high shear mixer. The wetted mass was extruded in a Nica E 140 extruder with a 0.6 mm screen size. The extrudate was spheronized in a lab unit until the surface was smooth and the cores were spherical. The cores were dried in a Glatt GPCG fluid-bed for approximately 30 minutes at 50 °C. The dried cores were fractionated by screening through a lower screen of 600 μm and an upper screen of 800 μm.

Example 8

Preparation of cores with a swelling layer using powder layering

The present example illustrates the preparation of cores with a swelling layer using powder layering, as an alternative to using suspension coating.

1 kg cores as obtained from Example 7 were coated with 4 kg pre-sieved L-HPC LH-31 by layering while simultaneously spraying a binder solution in a Glatt GPCG fluid-bed equipped with a rotary processor as described in Example 3. The composition of the binder solution (5% w/w dry matter) is shown in table 10.

Table 10

Ingredients	Amount (g)
Hydroxypropyl cellulose L-/fine	100.0
Ethanol 99.9%	1900.0

Total	2000.0

In the coating process 400% w/w L-HPC was applied.

The coated cores were dried for 30 minutes with an inlet air temperature at 35 °C and a rotations rate on the disk at 350 rpm. The dried cores were fractionated by screening through a lower screen of 710 µm and an upper screen of 1000 µm.

Example 9

Preparation of cores containing Levamisole for colon delivery

2 kg of cores from Example 8 were coated with a water insoluble coat and an enteric coat in a Glatt GPCG 3 fluid-bed equipped with a rotary processor as described in Examples 4 and 5. The coated cores were screened through a 1200 µm screen. Oversized material: <5% w/w.

Example 10

Preparation of a Levamisole modified release composition made in the form of tablets containing multiple units

Cores from Example 9 were mixed in a cubic mixer with granulate as known per se. The composition of granulate with the cores is shown in table 11.

Table 11

Ingredients	Amount (g)
Cores containing Levamisole	1500.0
Microcrystalline cellulose	750.0
Sodium carboxymethyl starch	125.0
Magnesium stearate	12.5
Talc	112.5
Total	2500.0

Tablets were produced from this granulate by the use of a Fette exacta compression machine. The mass of the tablets was approximately 250 mg.

Example 11

Preparation of cores with swelling agent mixed with a solid dispersion matrix of HPMC and Indomethacin

1 kg Cellulose Spheres with a particle size between 350-500 µm were coated with 1 a suspension containing a swelling agent a dissolved HPMC and Indomethacin solution and 2 an outer coat in a Glatt GPCG fluid-bed equipped with a rotary processor as described in Example 3. The composition of the coat (25.1% w/w dry matter) is shown in table 12. The outer coat composition of Example 3 was used.

Table 12

Ingredients	Amount (g)
L-HPC LH-31	4472.0
Indomethacin	15.0
Hydroxypropyl methylcellulose	903.0
Ethanol 99.9%	8056.0
Dichloromethane	8054.0
Total	21500.0

In the coating process 400% w/w L-HPC, 1.35% w/w Indomethacin as dispersion and 1% w/w outer coat were applied.

The dried cores were fractionated by screening through a lower screen of 710 µm and an upper screen of 1000 µm.

Example 12

Preparation of cores containing Indomethacin for colon delivery

2 kg of cores obtained from Example 11 were coated with a water insoluble coat and an enteric coat in a Glatt GPCG 3 fluid-bed equipped with a rotary processor as described in Example 4 and 5. The coated cores were screened through a 1200 µm screen. Oversized material: <5% w/w.

Example 13

Preparation of Indomethacin modified release composition made in the form of capsules containing multiple units

Indomethacin modified release product was prepared by filling cores as obtained form Example 12 into hard gelatine capsules. The mass of the capsules was approximately 200 mg.

Example 14

Preparation of tablets containing Insulin for colon delivery

The present example illustrates the preparation of tablets for colon delivery. The composition of the tablets is shown in table 13.

Table 13

Ingredients	Amount (g)
Insulin (lyophilised rh insulin)	1625.0
Microcrystalline cellulose	375.0
Sodium carboxymethylcellulose	375.0
Magnesium stearate	12.5
Talc	112.5
Total	2500.0

The ingredients were mixed in a cubic mixer and the mixture was compressed into tablets by the use of a Fette exacta compression machine.

2 kg of these tablets were coated with a water insoluble coat and an enteric coat in a Glatt GPCG 3 fluid-bed with a 2.0 mm spray nozzle and a spray pressure of 2.5 bars. The composition of the coatings is shown in table 6 and 7.

In the coating process 15% w/w water insoluble and 10% w/w enteric coat were applied.

The dew point of the process air was adjusted to an interval from 11 to 14 °C. The tablets were heated to 30 °C and throughout the coating process the product temperature was maintained substantially in the interval from 28 to 31 °C by adjustment of the liquid flow rate in the interval from 10 to 20 g/min. The inlet air temperature and the process airflow were kept at approximately 35 °C and 150 m^3/h, respectively. After the application of the coatings the coated tablets were dried for 15 minutes. The mass of the tablets was approximately 2 g.

Example 15

Preparation of cores with swelling agent mixed with lyophilized rhPTH, 4-MOAC and Chitosan-EDTA conjugate using powder layering

1 kg Cellulose Spheres with a particle size between 350-500 µm were coated with a pre-sieved mixture of 120 g lyophilized rhPTH (1-84) 600 g 4-MOAC, 540 g Chitosan-EDTA and 3.74 kg L-HPC LH-31 by layering while simultaneously spraying a binder solution in a Glatt GPCG fluid-bed equipped with a rotary processor. The composition of the binder solution (5% w/w dry matter) is given in Table 10. In the coating process 2% w/w rhPTH, 10% w/w 4-MOAC, 9% w/w Chitosan-EDTA, 374% w/w L-HPC and 1% w/w outer coat were applied (based on the weight of the core). The binder solution was also used as outer coat.

The cores were coated as described in Example 1 with the exception that the inlet air was humidified. The dew point was in the interval from 3 to 5 °C. The cores were heated to 25 °C and throughout the coating process the product temperature was kept at approximately 15 °C by adjustment of the liquid flow rate in the interval from 35 to 45 g/min. The inlet air temperature and the process airflow were kept at approximately 25 °C and 100 m^3/h, respectively. The coated cores were dried to water content below 2% w/w on trays at 30°C. The dried cores were fractionated by screening through a lower screen of 750 µm and an upper screen of 1000 µm. The content of rhPTH was at least 95% w/w.

Example 16

Preparation of cores containing lyophilized rhPTH, 4-MOAC and Chitosan-EDTA conjugate for colon delivery

2 kg of cores from Example 15 were coated with a water insoluble coat (applying 40% w/w) and an enteric coat (applying 20% w/w) in a Glatt GPCG 3 fluid-bed equipped with a rotary processor as described in Examples 4 and 5. The coated cores were screened through a 1.2 mm screen. Oversized material: <5%.

Example 17

Preparation of Parathyroid Hormone (PTH) modified release composition made in the form of capsules containing multiple units

Once daily PTH product (4 mg) to take in addition to a supplement of 1000-1500 mg Calcium and 400-1200 IU Vitamin D_3 (e.g. 1-3 Calcichew-D_3). The modified release

product was prepared by filling cores as obtained form Example 16 into hard gelatine capsules. The mass of the capsules was approximately 350 mg.

Example 18

Preparation of cores containing Calcium Carbonate and Vitamin D_3

The cores were prepared by the use of the extrusion/spheronization technique. The composition of the cores is shown in Table 14.

Table 14

Ingredients	Amount (g)
Cholecalciferol	50
Calcium carbonate	2000
Microcrystalline cellulose	400
Sodium carboxymethylcellulose	50
Purified water	1000

The ingredients were mixed and wetted in a Fielder high shear mixer. The wetted mass was extruded in a Nica E 140 extruder with a screen size between 1.0 mm. The extrudate was spheronized in a lab unit until the surface was smooth and the cores were spherical. The cores were dried in a Glatt GPCG fluid-bed for approximately 30 minutes at 50°C. The dried cores were fractionated by screening through a lower screen of 1000µm and an upper screen of 1200 µm.

Example 19

Preparation of a combinations product containing Calcium Carbonate, Vitamin D_3 and PTH in the form of capsules containing multiple units

Once daily product containing 500 mg calcium, 3200 IU vitamin D_3 and 4 mg PTH. The product was prepared by filling cores obtained form Examples 16 and 18 into hard gelatine capsules. The mass of the capsules was approximately 1900 mg. Alternatively, the cores were compressed into tablets.

CLAIMS

1. A pH and time-controlled drug delivery system for oral use comprising one or more of a first type of unit, the first type of unit comprising a therapeutically, prophylactically and/or diagnostically active substance, and the first type of unit having a layered structure of at least

i) an inner core
ii) a time-controlled layer surrounding the inner core,
iii) a film coating applied on the time-controlled layer, wherein the film coating is substantially water insoluble but permeable to an aqueous medium, and
iv) an outer layer of an enteric coating,

wherein the release of the active substance from the unit - when tested *in vitro* as an average of at least three determinations - is not more than about 10% w/w at a first pH value below about 4.0, and at a second pH value of from about 5.0 to about 8.0 the active substance is released in such a manner that - after a lag time of from about 0.5 to about 8 hours in which first time period not more than about 10% w/w of the active substance is released - at least about 50% w/w of the active substance contained in the unit is released within a second time period of not more than about 2 hours.

2. A system according to claim 1, wherein the release of the active substance from the unit – when tested *in vitro* – is not more than about 7.5% w/w such as, e.g., not more than about 5% w/w, not more than about 4% w/w, not more than about 3% w/w, not more than about 2% w/w or not more than about 1% w/w at the first pH value below about 4.0.

3. A system according to claim 1 or 2, wherein the first pH value is below about 3.5, such as, e.g., below about 3.0, below about 2.5, below about 2.0, below about 1.5 or a pH value corresponding to that of 0.1 N HCl.

4. A system according to any of the preceding claims, wherein the lag time is from about 1.0 to about 7 hours such as, e.g., from about 1.5 to about 6 hours, from about 2.0 to about 5 hours or from about 2.5 to about 4.5 hours or from about 2.5 to about 4 hours.

5. A system according to any of the preceding claims, wherein – after said lag time - at least about 60% w/w such as, e.g., at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w or at least about 90% w/w of the active

substance contained in the unit is released within the second time period of not more than about 2 hours.

6. A system according to any of the preceding claims, wherein said second time period is not more than about 90 min such as, e.g., not more than about 60 min, not more than about 50 min, not more than about 45 min, not more than about 40 min, not more than about 35 min, not more than about 30 min, not more than about 25 min, not more than about 20 min, not more than about 15 min, not more than about 10 min of not more than about 5 min.

7. A system according to any of the preceding claims, wherein the active substance in the unit is contained in one or more of the layers i) - iii) and/or in a further layer v) surrounding the inner core.

8. A system according to claim 7, wherein the active substance is contained in the further layer v).

9. A system according to claim 8, wherein the further layer v) is situated between layer i) and ii).

10. A system according to any of the preceding claims, wherein the active substance is subject to colon absorption and/or exerts its effect in the colon.

11. A system according to any of the preceding claims, wherein the enteric coating comprises an enteric polymer that has a pH cut off of at the most about 8.0 such as, e.g. in a range of from about 4 to about 7.5, in a range of from about 4.5 to about 7.0, from about 4.9 to about 6.9, from about 5.0 to about 6.5, from about 5.0 to about 6.3, from about 5.0 to about 6.0, from about 5.0 to about 5.9, from about 5.0 to about 5.7, from about 5.0 to about 5.6 or from about 5.0 to about 5.5.

12. A system according to any of the preceding claims, wherein the enteric coating comprises an enteric polymer selected from the group consisting of:
Amylose acetate phthalate, cellulose acetate phthalate CAP (pH cut off about 6.2), cellulose acetate succinate, cellulose acetate trimellitate CAT (pH cut off about pH 5.0), carboxymethyl ethylcellulose, formalin treated gelatine, hydroxypropyl methylcellulose acetate succinate HPMCAS (cut off pH about 5.0-5.5), hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose phthalate HPMC-P (cut off pHs about

5.0 and about 5.5), methacrylic acid copolymer (Eudragit L) (cut off pHs about 5.5 and about 6), methacrylic acid copolymer (Eudragit S) (cut off pH about 7), methacrylic acid copolymer (Eudragit FS) (cut off pH about 7.5), polyvinyl acetate phthalate PVAP (sureteric), shellac, starch acetate phthalate, styrene-Maleic acid copolymer, zein, and mixtures thereof.

13. A system according to any of the preceding claims, wherein the core is selected from pharmaceutically acceptable beads, spheres, granules, granulates, and pellets.

14. A system according to any of the preceding claims, wherein the core is selected from calcium alginate beads, cellulose spheres, charged resin spheres, glass beads, polystyrene spheres, sand silica beads or units, sodium hydroxide beads, sucrose spheres, and collagen-based beads.

15. A system according to any of claims 1-13, wherein the core is made of crystals of an active substance.

16. A system according to claim 14, wherein the core is selected from cellulose spheres and sucrose spheres.

17. A system according to claim 14, wherein the core is a collagen-based bead.

18. A system according to claim 14 or 17, wherein the collagen-based bead is made of material derived from animals such as, e.g., horses, pigs, cows, etc., or from recombinant, transgene, synthetic or semi-synthetic material.

19. A system according to any of the preceding claims, wherein the time-controlled layer comprises a substance that is swellable, osmotic and/or effervescent.

20. A system according to claim 19, wherein contact of the swellable, osmotic and/or effervescent substance with an aqueous medium results in disruption or destruction of the film coating layer iii).

21. A system according to claim 19 or 20, wherein the time-controlled layer is a swellable layer that swells upon contact with an aqueous medium.

22. A system according to claim 21, wherein the lag time is controlled by the time it takes for the swellable layer to swell to such an extent that the film coating layer is disrupted or destructed.

23. A system according to any of the preceding claims, wherein the lag time is controlled by the thickness and/or composition of the time-controlled layer.

24. A system according to any of the preceding claims, wherein the lag time is further controlled by the thickness and/or composition of the film coating layer.

25. A system according to any of claims 20-24, wherein the disruption or destruction of the film coating layer iii) is substantially independent of pH.

26. A system according to any of the preceding claims, wherein the film coating comprises a water insoluble polymer selected from the group consisting of:
Ammonio methacrylate copolymer (Eudragit RL, Eudragit RS), cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose butyrate, cellulose propionate, cellulose valerate, crospovidone, ethyl cellulose, hydroxypropylcellulose, hydroxyethylcellulose, polyacrylate dispersion (Eudragit NE), polydiethylaminomethylstyrene, polymethylstyrene, polyvinyl acetate, polyvinyl formal, polyvinyl butyryl, wax, and mixtures thereof

27. A system according to claim 26, wherein the water insoluble polymer creates a relatively non-flexible film coating.

28. A system according to claim 26 or 27, wherein the water insoluble polymer has a relatively short chain length.

29. A system according to any of the preceding claims, wherein the film coating layer iii) comprises ethyl cellulose and/or hydroxypropylcellulose.

30. A system according to claim 29, wherein the film coating layer iii) comprises ethyl cellulose that has a viscosity of at the most about 20 cps.

31. A system according to any of the preceding claims, wherein the film coating layer iii) comprises an additive that modifies disruption or destruction of the film coating layer upon exposure to an aqueous medium.

32. A system according to claim 31, wherein the additive modifies disruption or destruction of the film coating layer upon exposure to an aqueous medium.

33. A system according to any of the preceding claims, wherein any of the layers such as, e.g. the film coating layer iii) and/or the enteric coating layer iv) comprises an additive selected from the group consisting of:
Acetylated monoglyceride, acetyltributyl, acetyltributyl citrate, acetyltriethyl citrate, benzyl benzoate, calcium stearate, castor oil, cetanol, chlorebutanol, colloidal silica dioxide, Cutina, dibutyl phthalate, dibutyl sebacate, diethyl oxalate, diethyl malate, diethyl maleate, diethyl malonate, diethyl fumarate, diethyl phthalate, diethyl sebacate, diethyl succinate, dimethylphthalate, dioctyl phthalate, glycerin, glyceroltributyrate, glyceroltriacetate, glyceryl behanate, glyceryl monostearate, hydrogenated vegetable oil, lecithin, leucine, magnesium silicate, magnesium stearate, paraffin, polyethylene glycol, propylene glycol, polysorbate, silicone, stearic acid, talc, titanium dioxide, triacetin, tributyl citrate, triethyl citrate, zinc stearate, wax, and mixtures thereof.

34. A system according to any of claims 31-33, wherein the additive is a polyethylene glycol, magnesium stearate and/or paraffin.

35. A system according to any of the preceding claims, wherein the time-controlled layer ii) comprises a swelling agent selected from the group consisting of:
Alginic acid, alginates, carboxymethylcellulose calcium, carboxymethylcellulose sodium (Ac-Di-Sol), crospovidone, hydroxypropylcellulose, hydroxypropylmethylcellulose (HPMC), low substituted hydroxypropylcellulose (L-HPC), microcrystalline cellulose, polacrilin potassium, polyacrylic acid, polycarbofil, polyethylene glycol, polyvinylacetate, polyvinylpyrrolidone, polyvinylpyrrolidone, plasdone, sodium croscarmellose, sodium starch glycolate (Explotab), starches, and mixtures thereof.

36. A system according to any of the preceding claims, wherein the time-controlled layer ii) comprises an effervescent agent selected from alkali metal carbonates, alkali metal hydrogen carbonates, alkaline earth metal carbonates, alkaline earth metal hydrogen carbonates, citric acid, tartaric acid, fumaric acid, etc., and mixtures thereof.

37. A system according to any of the preceding claims, wherein the time-controlled layer ii) comprises an osmotic agent such as, e.g., sodium chloride and/or sorbitol.

38. A system according to any of the preceding claims, wherein the active substance is present in the form of a solid dispersion.

39. A system according to any of the preceding claims, wherein the active substance is dispersed in the time-controlled layer.

40. A system according to any of the preceding claims further comprising one or more pharmaceutically acceptable excipients.

41. A system according to claim 40, wherein the pharmaceutically acceptable excipient is selected from the group consisting of fillers, diluents and binders.

42. A system according to claim 40 or 41, wherein the pharmaceutically acceptable excipient is selected from the group consisting of:
Agar, alginate e.g. sodium alginate, calcium bicarbonate, calcium carbonate, calcium hydrogen phosphate, calcium phosphate, calcium sulphate, carboxyalkylcellulose, cellulose, charged sodium polystyrene sulphonate resin, dextran, dextrates, dextrin, dextrose, dibasic calcium phosphate (Emcompress), ethyl cellulose, fructose, gelatine, glucose, glyceryl palmitostearate, gummi arabicum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose, lactitol, lactose, magnesium carbonate, magnesium chloride, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, methylcellulose, microcrystalline cellulose, modified starches, polyethylene glycol, polyethylene oxide, polysaccharides e.g. dextran, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone/vinyl acetate copolymer, sorbitol, soy polysaccharide, sodium carbonate, sodium chloride, sodium phosphate, starch, sucrose, xylitol, and mixtures thereof.

43. A system according to any of the preceding claims, wherein the pharmaceutically acceptable excipient is selected from the group consisting of stabilizing agents, wetting agents, taste-masking agents, pH-adjusting agents, preservatives, antioxidants, dispersing agents, and enhancers.

44. A system according to claim 43, wherein the pharmaceutically acceptable excipient is one or more enhancers.

45. A system according to any of the preceding claims in the form of a multiple unit composition.

46. A system according to any of claims 1-44 in the form of a single unit composition.

47. A system according to any of claims 1-45 further comprising a second type of units comprising the same and/or a different active substance and the first and second types of units being designed to release the active substance(s) with different release rates.

48. A system according to claim 47 further comprising a third type of units comprising the same and/or a different active substance and the first, second and types of units being designed to release the active substance(s) with different release rates.

49. A system according to claim 47 or 48, wherein the second and/or third type of units is designed to release the active substance in a controlled manner

50. A system according to claim 47 or 48, wherein the second ad/or third type of units is designed to release the active substance relatively fast from the system upon oral administration.

51. A system according to any of claims 47-50 comprising a mixture of units of the first, second and third types, wherein units of the first type are designed to release the active substance in the colon, units of the second type are designed to release the active substance in sustained manner and units of the third type are designed to release the active substance in a relatively fast manner upon oral administration.

52. A system according to any of the preceding claims, wherein layer ii) is contained in admixture with layer i).

53. A system according to any of the preceding claims comprising a further therapeutically, prophylactically and/or diagnostically active substance.

54. A system according to any of the preceding claims, wherein the first type of units comprises a further active substance.

55. A system according to any of the preceding claims comprising as active substance midodrine and/or desglymidodrine of a pharmaceutically acceptable salt thereof.

56. A system according to any of the preceding claims, wherein the *in vitro* release is determined employing an *in vitro* dissolution method according to USP or Ph.Eur.

57. A system according to claim 55 and 56, wherein the *in vitro* release of midodrine and/or desglymidodrine is as described herein.

58. A system according to any of claims 1-54 comprising as an active substance PTH or a fragment, analog or derivative thereof.

59. A system according to any of claims 1-54 comprising as an active substance a calcium containing compound.

60. A system according to any of claims 1-54 comprising as an active substance a vitamin D.

61. A system according to claim 58 or 59 comprising i) PTH or a fragment, analog or derivative thereof, and ii) a calcium containing compound as active substances.

62. A system according to any of claims 58-60 comprising i) PTH or a fragment, analog or derivative thereof, ii) a calcium containing compound as active substances, and iii) a vitamin D as active substances.

63. A system according to claim 58 or 60 comprising i) PTH or a fragment, analog or derivative thereof, and ii) a vitamin D as active substances.

64. A system according to claim 59 or 60 comprising i) a calcium containing compound and ii) a vitamin D as active substances.

65. A method for administering active substances to the colon, the method comprises administering to a patient a sufficient amount of a drug delivery system according to any of claims 1-64.

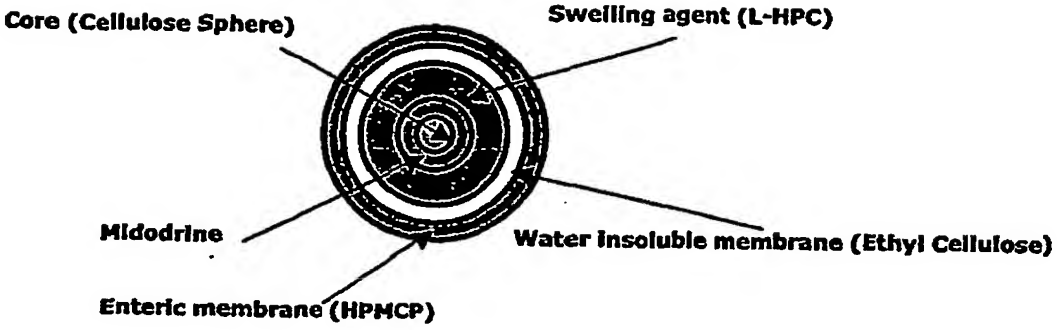

Fig. 1